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THE CHEMISTRY OF ORGANIC COMPOUNDS

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THE CHEMISTRY OF ORGANIC COMPOUNDS

A YEAR'S COURSE IN ORGANIC CHEMISTRY

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THIRD EDITION

THE MACMILLAN COMPANY · NEW YORK · 1948

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PREFACE

This book is a complete revision of the 1939 edition of *The Chemistry of Organic Compounds;* it is the joint product of two authors. We have felt that the time has come in teaching organic chemistry to alter in certain respects the conventional approach to reaction rates and equilibria. Practicing organic chemists will agree that these two subjects lie at the root of any realistic discussion of the behavior of the carbon compounds in the laboratory or in industry. Today when so many industrial processes depend on the ability of the chemist to operate at high temperatures, the relation between temperature and equilibrium constant is particularly important. We have therefore introduced gradually the basic physicochemical principles underlying chemical equilibria. We have done this without introducing those considerations in physical chemistry which are associated with the terms free energy and entropy. We believe that with the aid of certain rules and principles carefully stated in the text it is possible for even a beginning student to understand in a general way how energy relations control equilibria. Of course underlying such a presentation as we have just described there must be constant emphasis on the difference between rates and equilibria. This is a theme recurring throughout the book.

The introduction of new physicochemical concepts and data (including an expansion of the earlier treatment of the electronic theory of valence and of resonance) has been accomplished, we believe, without interfering with the arrangement of material which characterized the earlier editions. We have retained the basic idea that new material should be introduced on a sound pedagogical rather than a formal basis. In bringing the whole treatment up to date much new material from industrial chemistry has been introduced. Recent developments connected with the aliphatic hydrocarbons in particular have been included because these developments are of such importance in the preparation of liquid fuels and synthetic rubber. In spite of all the new material, the book is not materially larger than the previous edition. We have condensed the treatment of certain less important topics and have eliminated a few minor topics.

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Throughout the book small changes in the presentation have been made in order to gain effectiveness.

The rapid expansion of the fields of biochemistry and pharmacology in the last decade poses a serious problem to the authors of a book of this type. It is impossible to include all the compounds which are of interest to the general public in connection with medicine and public health. Furthermore we doubt the educational value of the mere inclusion of structural formulas of a great variety of complex substances. We have tried to cover the major topics and to relate the chemistry of the compounds considered to the principles expounded in this book. Considerable space has been devoted to a few basic biological processes which have been elucidated sufficiently to enable a fairly complete account of the mechanism to be presented. Other processes where our ignorance is still very great have only been mentioned. Even for students who are going on to specialize in biology or medicine we think this choice of material provides the soundest basis.

James B. Conant
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FOREWORD

Organic chemistry is the chemistry of the compounds of carbon. At first sight, it seems strange that one element should be singled out for special attention, and stranger still, perhaps, that this branch of chemistry should be considered important enough to be one of the two major divisions of the subject. No other element shares this honor with carbon; all the rest of chemistry is classed together under the one heading, inorganic chemistry.

The origin of the name suggests one of the reasons for the importance of organic chemistry: originally the science dealt with the products of plant and animal life. It was long believed that these were in some mysterious way different from the lifeless rocks and minerals with which inorganic chemistry dealt. The distinction was shown to be false by the synthesis from inorganic materials of several natural products. This barrier between the two chemistries was thus broken down and it was recognized that the fundamental laws and principles of both were identical. Since almost all the important substances produced by animate nature contain carbon, the name *organic chemistry* was transferred to the study of the compounds of this element.

While organic chemistry, today, is still concerned with compounds produced by plants and animals and is thus closely allied with biochemistry, it also deals with many other substances. Many of these are derived from petroleum and coal tar and are of great industrial importance. Thus the work of the organic chemist touches that of the biologist and the doctor on the one hand, and that of the chemical engineer in such industries as petroleum, rubber, and the coal-tar dyes and drugs on the other.

Many of those who make the acquaintance of organic chemistry on their way to other callings will be impressed chiefly by its applications to medicine and technology. These applications are possible, however, only as a result of the remarkable development of the science of organic chemistry in the last hundred years. This scientific development is to many as remarkable an achievement as are the technical applications. The two cannot be separated, however, and both have been kept in mind in writing this book.

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Chapter 1

THE ALCOHOLS

Composition of Ethyl Alcohol. Ethyl alcohol is a substance of such great practical importance that we may well choose it as the starting point in a study of organic chemistry. Let us center our attention first on a chemical investigation of its constitution. The first step in such a study involves the careful purification of the compound, and the second, the qualitative and quantitative analysis. A discussion of these fundamental methods will be found in a laboratory manual of organic chemistry and we may therefore turn directly to the results. Pure ethyl alcohol is a liquid boiling at 78°; a quantitative analysis shows that it contains carbon, hydrogen, and oxygen in such amounts as correspond to the existence of two carbon atoms, six hydrogen atoms, and one oxygen atom.

THE DETERMINATION OF THE EMPIRICAL FORMULA OF ETHYL ALCOHOL

Results of Quantitative Analysis

Element	*Per Cent*	*Atomic Weight*	*Atomic Ratio*	*Ratio of Atoms*
Carbon	52.18	÷ 12	= 4.35	4.35 ÷ 2.17 = 2
Hydrogen	13.04	÷ 1	= 13.04	13.04 ÷ 2.17 = 6
Oxygen	34.78	÷ 16	= 2.17	2.17 ÷ 2.17 = 1

The **empirical formula** is therefore C_2H_6O. Such a formula tells us only the relative number of atoms in the molecule. To establish the **molecular formula** of a compound we must determine its molecular weight. This is readily done by finding the density of the vapor or by noting the depression of the freezing point (or elevation of the boiling point) of a suitable solvent in which a weighed amount of the substance has been dissolved. The results of many such experiments have shown that the molecular weight of ethyl alcohol is 46. The molecular formula of ethyl alcohol is therefore C_2H_6O ($2 \times 12 + 6 + 16 = 46$).

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Isomerism. In an elementary study of inorganic chemistry we should hail this result with satisfaction, since the determination of the kind and number of atoms in the molecule is usually sufficient to establish an adequate formula; for example NH_3, HCl, H_2O_2. These are called *molecular formulas*. Quite the reverse is true in organic chemistry: such formulas are inadequate in dealing with the compounds of carbon. This may be illustrated by a simple example. **Methyl ether,** a gas related to the ether used in anesthesia, has exactly the same percentage composition and the same molecular weight as ethyl alcohol. Therefore it must be also represented by the formula C_2H_6O. There can be no doubt about the difference between these compounds, since one is a liquid boiling at 78° and is soluble in water, while the other is a gas at room temperature and is insoluble in water. Their chemical reactions are also entirely different. *Two compounds which have the same molecular formula are said to be* **isomers;** the phenomenon is known as *isomerism.*

The Necessity for Structural Formulas. Isomerism is very common in organic chemistry. For example, twenty-six isomers with the formula $C_6H_{14}O$ have been prepared and their properties recorded. It is obvious that unless the organic chemist is able to write formulas which represent the differences between isomers, he is in a hopeless position. It was not until about the middle of the last century that a satisfactory method of formulating organic compounds was developed; before this time the chemistry of the carbon compounds was in a confused state. After the introduction of structural formulas, organic chemistry advanced by leaps and bounds. The chief name associated with the remarkable advancement in this field of chemistry is that of Kekulé.[1]

The Theory of Linkages. The theory which was advanced to explain the differences between the various isomers may be called the *theory of atomic linkages.* This assumes that isomerism is due to the different ways in which the same atoms are joined together in the molecule. The organic chemist, thus, seeks to express in his structural formulas not only the number and kinds of atoms in the molecule but *the way in which they are linked together.* In other words his formulation must represent the structure of the compound. Let us see how this may be done for ethyl alcohol.

[1] Friedrich August Kekulé (1829–1896). Professor of Chemistry at the University of Bonn.

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Hydroxyl Group in Alcohols. Ethyl alcohol is very similar to water in many of its chemical properties, as is illustrated by their reactions with metallic sodium and phosphorus trichloride.

$$1.\ \begin{array}{ll} \text{(a)}\ 2H_2O + 2Na & \longrightarrow 2HONa + H_2 \\ \text{(b)}\ 2C_2H_6O + 2Na & \longrightarrow 2C_2H_5ONa + H_2 \end{array}$$

$$2.\ \begin{array}{ll} \text{(a)}\ 3H_2O + PCl_3 & \longrightarrow 3HCl + P(OH)_3 \\ \text{(b)}\ 3C_2H_6O + PCl_3 & \longrightarrow 3C_2H_5Cl + P(OH)_3 \end{array}$$

It will be noticed that in the first two reactions, sodium hydroxide and a compound, C_2H_5ONa (sodium ethoxide), are formed by the replacement of one hydrogen atom of the molecule. In the second set of reactions, the phosphorus atom becomes attached to an hydroxyl group which in one case has been removed from water and in the other must come from the alcohol. The facts of inorganic chemistry show that the atoms in the water molecule must be arranged H − O − H; the existence of the hydroxyl group (OH) is evident. Since the phosphorous acid is formed from alcohol as well as from water (equations 2a, 2b), we may conclude with considerable assurance that *ethyl alcohol has an hydroxyl group.*

These two reactions are also characteristic of another well-known substance, **methyl alcohol.** This compound (commonly called *wood alcohol*) has the molecular formula CH_4O as determined by the analysis and vapor density of a carefully purified sample. Since it reacts with sodium evolving hydrogen, and with phosphorus trichloride forming phosphorous acid, $P(OH)_3$, we conclude that it also contains an hydroxyl group. We may, therefore, write the formulas CH_3OH for methyl alcohol and C_2H_5OH for ethyl alcohol. These formulas, however, are still not perfectly clear. How are the carbon and hydrogen atoms arranged in the groups CH_3 and C_2H_5?

Structure of Methyl and Ethyl Alcohols. The founders of the structural theory assumed that in organic compounds carbon always has a valence of four, oxygen of two, and hydrogen of one. With this as a basis the question just raised concerning the structure of methyl alcohol is easily answered. *There is only one possible arrangement of the atoms in* CH_3OH, and that is, the three hydrogen atoms must be attached to the lone carbon and this, in turn, must be bound to the hydroxyl group. Thus we have a complete **structural** or **graphical formula.**

The dash (−), whether vertical or horizontal, stands for a valence

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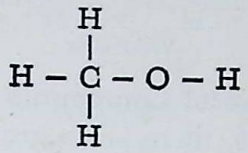
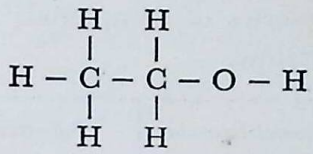
bond, a link, which joins the atoms together. There are four bonds from the carbon atom, two from the oxygen atom, and only one from



each hydrogen atom. Applying the same principles, the complete structural formula of ethyl alcohol is



By attempting to write a variety of structural arrangements for ethyl alcohol it is easy to convince oneself that there is only one way of writing C_2H_5OH, *provided* that the valence of hydrogen is one, oxygen two, and carbon four. It is, of course, immaterial whether the formula be written from right to left or left to right or at what angle the various atoms are connected. The structural formula simply says that the two carbon atoms in ethyl alcohol are joined to each other, and that one is attached to three hydrogen atoms, the other to two hydrogen atoms and the hydroxyl group.

Writing Structural Formulas. A study of a great variety of organic compounds has made certain the original assumption in regard to the valence of carbon, oxygen, and hydrogen. Carbon always has a valence of four, except in a few very unusual substances. Therefore, in writing structural formulas we must arrange the atoms in such a way that each carbon atom always is connected with four linkages, oxygen with two, and hydrogen with one. *Every formula should be tested by noting the valence of each atom.*

Structure of Methyl Ether. Methyl ether, spoken of above as the isomer of ethyl alcohol, reacts neither with phosphorus trichloride nor with sodium; therefore, it has *no* hydroxyl group. It has the following formula, which, it is easy to see, represents a molecule of an entirely different nature from that of ethyl alcohol. This case of isomerism is thus explained satisfactorily by the structural theory.

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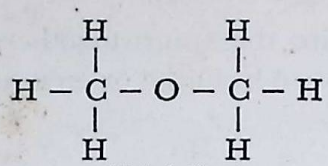

Methyl ether

The Alcohols as a Class of Compounds. Besides the well-known methyl and ethyl alcohols, there are a great many other substances which are called *alcohols* by the organic chemist. They all show the reactions which we have learned are characteristic of an hydroxyl group, and their structural formulas, therefore, must show the linkage $-O-H$. They form a graded series with an increasing number of carbon atoms. Such a series of compounds is called an *homologous series* and is illustrated below.

Name	*General Formula*	*Difference*	*Number of Isomers*
Methyl alcohol	CH_3OH		One substance
		$>CH_2$	
Ethyl alcohol	C_2H_5OH		One substance
		$>CH_2$	
Propyl alcohols	C_3H_7OH		Two substances
		$>CH_2$	
Butyl alcohols	C_4H_9OH		Four substances
		$>CH_2$	
Amyl alcohols	$C_5H_{11}OH$		Eight substances

We may define an homologous series as a series of similar compounds in which *each member differs from the one below it and the one above it by CH_2*. It will be noted that all the compounds of this series correspond to a **general formula** $C_nH_{2n+1}OH$. That is, the number of hydrogen atoms (not including that of the OH group) is one more than twice the carbon atoms.

Isomeric Propyl and Butyl Alcohols. When we come to the substance C_3H_7OH in the homologous series of alcohols, we find that *more than one substance is represented by the formula.* In other words, a more subtle type of isomerism is now at hand. The reason for this is evident from a consideration of the complete structural formulas of such substances. Bearing in mind the rules in regard to the valence of

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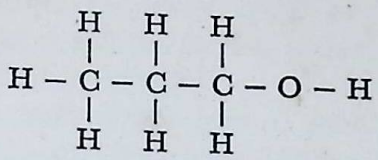
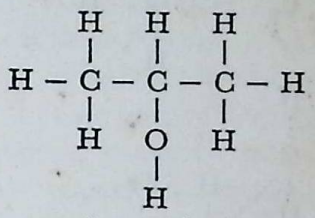
the different atoms and the fact that the substances all contain one hydroxyl group, we find that there are two and *only two* ways of arranging the atoms in C_3H_7OH; these are



Normal propyl alcohol

and

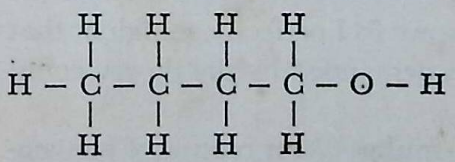


Isopropyl alcohol

These formulas are usually written as $CH_3CH_2CH_2OH$ and $CH_3CHOHCH_3$. There are actually two and *only* two substances C_3H_7OH; one is normal propyl alcohol boiling at 98°, the other is isopropyl alcohol which boils at 82°.

At first sight it might appear that there were many different ways of arranging the atoms in the molecule C_3H_7OH, all of which conformed to the rules of valence. That this is not so will be most quickly and convincingly demonstrated by actual trial with a pencil and paper. It will be remembered that the linkage of two carbon atoms through oxygen is excluded from the possibilities by the fact that the compound has an hydroxyl group; it is an alcohol. Hydrogen has only one valence bond and therefore cannot serve to join two other atoms together. Therefore the three carbon atoms must be joined in a chain. The position of the hydroxyl group is the only variable left. This group may be placed at the right end, in the center, or at the left end. The seven hydrogen atoms of C_3H_7OH now will be found sufficient to occupy the seven remaining bonds of the three carbon atoms. A moment's consideration will convince one that there is no difference between the two ends of this symmetrical chain of carbon atoms. Whether the hydroxyl group is written at the left end or the right end is without significance. Both arrangements represent the same linkage; they could be cut out and superimposed on each other by merely turning through 180°. The arrangement with the hydroxyl group in the center is different. This cannot be superimposed on the other formula because the hydroxyl group is attached to a carbon atom in the middle of the chain. Thus, in one formula we have the group $>CHOH$, in the other $-CH_2OH$.

The **isomerism of the butyl alcohols,** C_4H_9OH, is represented by the following structural formulas.



or $CH_3CH_2CH_2CH_2OH$ Normal primary butyl alcohol

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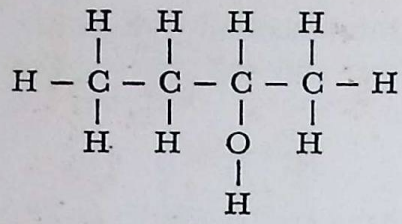
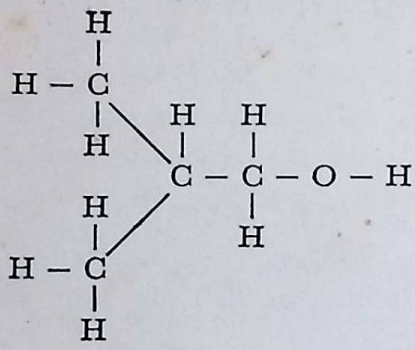
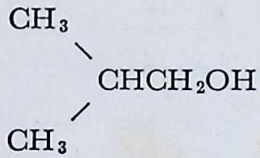


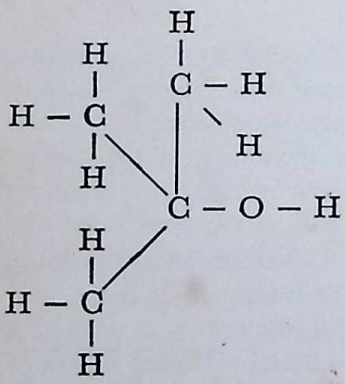
or $CH_3CH_2CHOHCH_3$ Normal secondary butyl alcohol



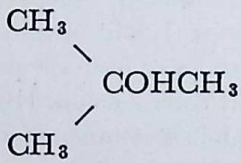
or



Primary isobutyl alcohol



or



Tertiary butyl alcohol

Thus, with the aid of the structural theory, we can predict the number of isomers which are possible in the case of the propyl alcohols and butyl alcohols, and test the prediction by experiment. Repeated trials in many laboratories have shown that such predictions of the structural theory are always verified. By working long enough and hard enough, it is always possible to make the number of isomers required by the theory, but more than this number have never been found. Since the number of isomers increases very rapidly as one goes up an homologous series, many isomers of the higher members have not yet been prepared. However, since our experimental facts and the predictions of the structural theory coincide so precisely in the lower members of this and other series, we feel perfectly confident that in time exactly the number of isomers demanded by the theory could be prepared in each case.

Conventions Used in Writing Formulas. As a matter of convenience, organic chemists have agreed to write their structural formulas

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in a condensed form, and the student would do well to master the conventions employed. The extended formulas of the butyl alcohols which are printed on page 8 on the left (sometimes called *spider-web formulas*) are often useful at first in understanding the theory of linkages, but the student should use them as little as possible. The conventions used will be apparent from these examples; the usual formula is printed on the right. It should be noted that we write the group of carbon and hydrogen atoms after each other in straight-chain compounds and show their connection by bonds in branched-chain compounds; other groups or atoms follow the hydrogen.

Three-Dimensional Models. The theory of linkages was developed to explain the isomerism of organic compounds. The structures of many substances were deduced from their reactions and transformations very much as we have done for ethyl alcohol and dimethyl ether. In the last twenty years evidence as to the correctness of these conclusions of the organic chemist has accumulated as a result of the labors of physicists. For example, a measurement of the diffraction of X rays by crystals enables physicists to calculate the distances between the centers of the atoms in various compounds. Similarly, a study of the diffraction of an electron beam by gases leads to conclusions as to the interatomic distances in the molecules of which the gas is composed. As a result of all these studies we can construct three-dimensional models of the simple organic molecules with considerable assurance. Such physical measurements have proved a very valuable aid to the organic chemist in interpreting purely chemical evidence. Nowadays one should get used to thinking of formulas in three-dimensional terms early in the course. This can be done best by handling models built to scale. On paper we often depict the carbon atoms in such models as regular tetrahedra since the measurements of the physicists have shown what the chemist long suspected, that the four carbon valences were at angles to each other which corresponded to such an arrangement. The angle of the two valences of oxygen in both alcohol and ether is approximately 111°. The interatomic distances are very nearly constant and those we are interested in here are:

INTERATOMIC	DISTANCE	SUM OF RADII OF ATOMS
C – C	1.54 Å[1]	0.77 + 0.77 Å
C – H	1.07 A	0.77 + 0.30 A
C – O	1.43 A	0.77 + 0.66 A
O – H	0.96 A	0.66 + 0.30 A

[1] The Ångstrom unit, Å, is one one hundred millionth (10^{-8}) of a centimeter.

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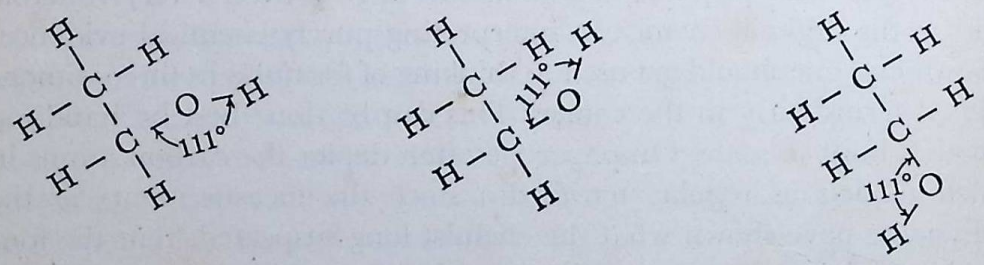
Such distances would result if the atomic radii were essentially the same in all related compounds and were as follows: carbon 0.77, oxygen 0.66, hydrogen 0.30. We shall see later that these radii are modified in certain types of compounds.

Construction of three-dimensional models will show that in all but the simplest compounds there are many ways in which the atoms in a chain may be placed with regard to each other. In the solid state there is one stable relation which is believed to correspond in most compounds to a zigzag chain. In the liquid form, in solution, or in gases, however, the molecules through thermal agitation take various shapes though certain configurations may be more favored than others. But the different shapes into which the same model can be twisted *do not correspond to different isomers.* This is an important point for the student to understand at the outset in considering the spatial arrangements of the atoms in a molecule.

For example, the different spatial relationships of the atoms in ethyl alcohol indicated below do not correspond to different substances. The energy required to change any one arrangement into another (a change which involves no breaking of bonds, only rotation about bonds) is so slight that all the molecules in a gas or a liquid or solution would never be lined up in this one way; rather they would be distributed at random among the many different spatial relations which would result by twisting the atoms with reference to each other.



These are three of the many spatial relationships of the atoms in a molecule of C_2H_5OH. They do not correspond to different substances. All the atomic distances and angles are the same, of course.

Because a model may be twisted into so many shapes, it is difficult to depict it on paper without implying that one relationship is more important than another. Therefore, we shall use pictures of three-dimensional models only occasionally and continue to use the two-dimensional formulas to represent the structures of almost all the organic compounds considered in this book. It is essential, however,

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for the student to construct three-dimensional models for himself and to learn to visualize organic structures in three dimensions.

Classification of Alcohols. Since there are only two isomeric propyl alcohols, it is possible to refer to them by using the terms *normal* and *iso*. By using the word *normal* to indicate a straight chain (abbreviated by *n*-, thus *n*-propyl alcohol) and the prefix *iso*- to denote a forked chain, a fairly satisfactory method of naming the butyl alcohols can also be developed. Furthermore, an examination of the various butyl alcohols will show that they can be arranged into the three following groups: (1) those having the grouping $-CH_2OH$ which are called *primary* alcohols; (2) those having the grouping $>CHOH$ which are called *secondary;* (3) those with the grouping $>COH$ which are designated as *tertiary* alcohols.

Naming Primary Alcohols. The first five normal straight-chain alcohols are named in the table below. The alcohols with six or more carbon atoms are named with a Greek prefix indicating the number of carbon atoms. For example, the normal alcohol $C_{10}H_{21}OH$ is *n*-decyl alcohol. The general formula for each group of alcohols is easily written by recalling that a general formula for the series is $C_nH_{2n+1}OH$.

Naming Secondary and Tertiary Alcohols. Where there are only a few isomers, it is possible to find simple names for the different isomeric alcohols as is done with the butyl alcohols given in the table on page 14. There is only one secondary and only one tertiary butyl alcohol. But higher in the series we get into difficulty. There are three secondary alcohols isomeric with *n*-amyl alcohol, $C_5H_{11}OH$. How are they to be named?

A convenient method of naming alcohols is to regard them as though they were built up by taking methyl alcohol, CH_3OH, and replacing one or more of the hydrogens of the CH_3 by groups of carbon and hydrogen atoms called *alkyl groups*. These groups in turn are named from the alcohol to which they are related. Thus the CH_3 group of methyl alcohol is known as the *methyl group*, the CH_3CH_2 or C_2H_5 of ethyl alcohol is known as the *ethyl group*, and so on.

The following are the common alkyl groups.

CH_3-	**Methyl group**
CH_3CH_2- or C_2H_5-	**Ethyl group**
$CH_3CH_2CH_2-$	**Normal propyl group**

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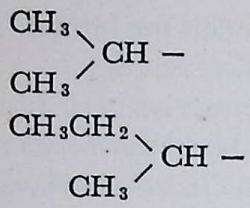
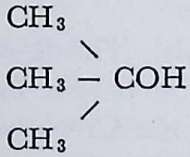


Isopropyl group

Sec.-butyl group

When we consider complex alcohols as derivatives of methyl alcohol, CH_3OH, this latter substance is called *carbinol*. We then name the alkyl groups which are attached to the carbon atom which holds the OH group. Such alkyl groups are *substituents* since they may be regarded as having been substituted in place of hydrogen atoms of the parent substance, CH_3OH or carbinol.

Trimethyl-carbinol is:

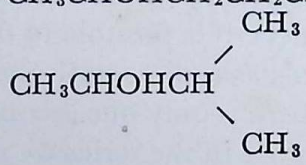


This is also written as $(CH_3)_3COH$.

The three isomeric secondary amyl alcohols are:

Methyl-propyl-carbinol, $CH_3CHOHCH_2CH_2CH_3$

Methyl-isopropyl-carbinol,



which is also written $CH_3CHOHCH(CH_3)_2$; and

Diethyl-carbinol, $CH_3CH_2CHOHCH_2CH_3$

For the sake of clarity, where there are a number of different alkyl groups hyphens are often used to separate the prefixes. It is equally correct to write an unhyphenated word, e.g., methylisopropylcarbinol; it is usually considered incorrect, however, to write methyl isopropyl carbinol. In this book we shall use hyphens whenever there are prefixes representing several substituents.

Physical Properties of Alcohols. If we compare the boiling points of the normal primary alcohols in the homologous series $C_nH_{2n+1}OH$, a very interesting gradual and regular change is noticed. This is illustrated below.

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PHYSICAL PROPERTIES OF NORMAL PRIMARY ALCOHOLS

Name	*Formula*	*Boiling Point*	*Density at 25°*	*Solubility Grams per 100 Grams of Water at 20°*
Methyl alcohol	CH_3OH	65°	0.792	∞
Ethyl alcohol	CH_3CH_2OH	78°	0.785	
Propyl alcohol	$CH_3CH_2CH_2OH$	98°	0.799	
Butyl alcohol	$CH_3CH_2CH_2CH_2OH$	118°	0.805	8.3
Amyl alcohol	$CH_3CH_2CH_2CH_2CH_2OH$	138°	0.816	2.6
Hexyl alcohol	$CH_3CH_2CH_2CH_2CH_2CH_2OH$	156°	0.820	Less than 1

The graph (Fig. 1) shows that for the *normal primary alcohols* there is a regular increase in boiling point with increasing number of carbon atoms. The higher members of the series are solids at room tempera-

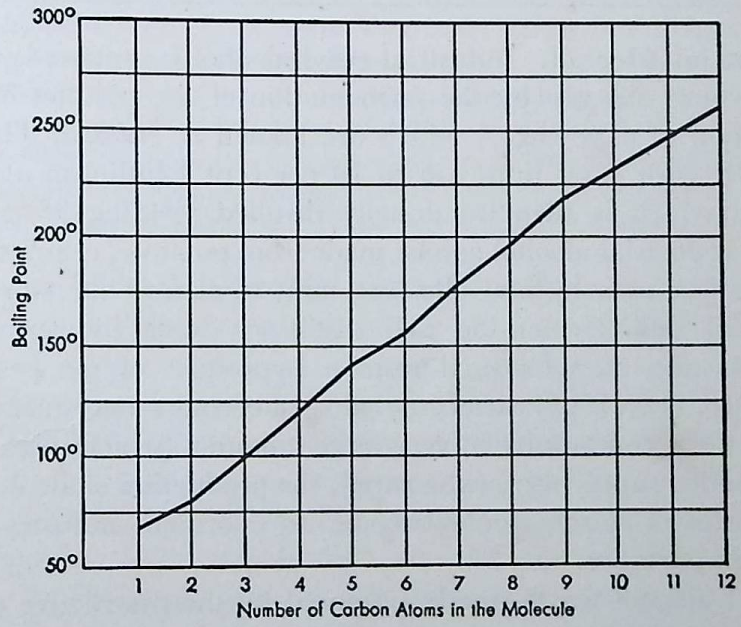

FIG. 1. The boiling points of normal primary alcohols from CH_3OH to $C_{12}H_{25}OH$.

ture. Thus *n*-decyl alcohol, $C_{10}H_{21}OH$, melts at 7°. The normal primary alcohol with the formula $C_{32}H_{65}OH$ melts at 89°.

The isomeric alcohols differ in boiling point as illustrated by the table just below. In general, for a group of isomeric alcohols, branching the carbon chain lowers the boiling point but increases the solubility in water.

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PHYSICAL PROPERTIES OF THE ISOMERIC BUTYL ALCOHOLS

Name	*Formula*	*Boiling Point*	*Density at 25°*	*Solubility Grams per 100 Grams of Water at 20°*
n-Butyl alcohol (butanol)	$CH_3CH_2CH_2CH_2OH$	118°	0.805	8.3
Isobutyl alcohol	$(CH_3)_2CHCH_2OH$	108°	0.804 (at 16°)	23
Secondary butyl alcohol	$\begin{matrix} CH_3CH_2 \\ \diagup \\ CHOH \\ \diagdown \\ CH_3 \end{matrix}$	100°	0.807	13
Tertiary butyl alcohol	$(CH_3)_3COH$	83°.	0.780	Completely miscible

Industrial Alcohol. Industrial ethyl alcohol is prepared today in America very largely by the fermentation of the residues from the purification of cane sugar, which are known as *molasses*. These are fermented with yeast until a 6 to 10 per cent solution of alcohol is obtained which is then fractionally distilled yielding 95 per cent alcohol. Industrial alcohol can be made from potatoes, grain, or other starchy substances by first allowing malt to change the starch into sugar and then fermenting and distilling. Some industrial ethyl alcohol is also manufactured from a byproduct of the petroleum industry (p. 118). If industrial ethyl alcohol becomes a substance which is used by the community in very large amounts (which might occur if the gasoline supply were exhausted), the production of alcohol from cheap forms of starch would become an enormous industry of the greatest importance.

Methyl alcohol was formerly prepared by the destructive distillation of wood and hence was called *wood alcohol*. It is now made industrially by the combination of hydrogen and carbon monoxide, a reaction which will be discussed in detail in Chap. 8.

Uses of Methyl and Ethyl Alcohol. At present, methyl and ethyl alcohols are used as starting materials for the manufacture of many other organic substances, since they are relatively cheap. They are also used widely as solvents, because they dissolve a great variety of substances which do not dissolve in water. The paint and varnish

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industry, for example, uses large quantities of both alcohols. The perfume, flavoring, and pharmaceutical industries use ethyl alcohol for preparing solutions of perfumes, flavors, and drugs. Extract of vanilla is an ethyl alcoholic solution of the flavoring constituent of the vanilla bean. Tincture of iodine is an ethyl alcoholic solution of iodine. Indeed, the words *extract* and *tincture*, when thus used, almost invariably denote ethyl alcoholic solutions. Because of its poisonous effect on the human system, methyl alcohol cannot be used for such purposes. Methyl and ethyl alcohols are widely used in antifreeze mixtures for automobiles.

Ethyl alcohol is subject to a very heavy tax in all countries, and its sale is strictly regulated in the United States. If it is made unsuitable for drinking by the addition of methyl alcohol or other substances, it can be sold tax-free in most countries, including the United States. Such alcohol is said to be *denatured*. Methyl alcohol is the principal substance used for denaturing ethyl alcohol. In addition, certain amounts of evil-smelling substances are often included in order to afford a warning that the liquid is poisonous. The use of specially denatured alcohol with only slightly poisonous ingredients is allowed under government supervision in the manufacture of pharmaceutical preparations and in certain other industries.

It is possible that, in the future, denatured alcohol may be used as a fuel for internal-combustion engines, but at present it is more expensive than gasoline. In relatively small quantities it is sold as a fuel for household use, in the form of *solid alcohol*. This is denatured alcohol containing a small amount of soap or nitrocellulose which causes the formation of a solid jelly.

Absolute Alcohol. Specially purified methyl and ethyl alcohols, free from water and other impurities, are known as *absolute methyl alcohol* and *absolute ethyl alcohol*. By careful distillation with a fractionating column, methyl alcohol can be obtained practically free from water. The last 5 per cent of water cannot be removed from ethyl alcohol in this way. It can be removed by boiling the 95 per cent alcohol with calcium oxide. The calcium oxide combines with the water, forming calcium hydroxide, and the alcohol is left unchanged and can be finally distilled. This is the method commonly employed in the laboratory. Industrially, absolute ethyl alcohol is prepared by taking advantage of the fact that a mixture of benzene (C_6H_6), water, and ethyl alcohol in the proportions 74.1 per cent benzene, 7.4 per cent water, 18.4 per cent alcohol distills at a lower temperature than any one of the three pure substances. Benzene is added to the 95 per cent alcohol, and the mixture carefully distilled; the first fraction (bp 65°) consists of the azeotropic mixture of benzene, water, and alcohol just mentioned. After all the water has thus been removed,

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the boiling point rises to about 68°, and the distillate is a mixture of alcohol and benzene; finally absolute alcohol distills at 78.3° and is collected. Absolute alcohol slowly absorbs water from the air, and must be kept carefully sealed in order to remain free from water.

Industrial Uses of Higher Alcohols. During the last twenty years the industrial production of some of the higher alcohols has been developed, and they have become substances of commercial importance. They are largely used as solvents either directly or in the form of their esters (compounds which are readily formed from the alcohols as will be described in Chap. 5). They are also used as the starting point in the manufacture of a number of other organic compounds of industrial importance. The most important higher alcohol from the industrial standpoint is ***n*-butyl alcohol (butanol)**, $CH_3CH_2CH_2CH_2OH$, prepared from cornstarch or from acetylene (p. 166). **Normal propyl alcohol,** $CH_3CH_2CH_2OH$, two secondary alcohols, **isopropyl alcohol,** $CH_3CHOHCH_3$, and **secondary butyl alcohol,** $CH_3CHOHCH_2CH_3$, and a tertiary alcohol, **tertiary butyl alcohol,** $(CH_3)_3COH$, as well as a number of the isomeric amyl alcohols, $C_5H_{11}OH$, are manufactured from petroleum and natural gas by processes which will be discussed later (Chap. 6). As yet none of them has attained the industrial importance of butanol.

Some normal alcohols of longer straight chains are now of industrial importance. Among these are lauryl alcohol, $C_{12}H_{25}OH$, cetyl alcohol, $C_{16}H_{33}OH$, and stearyl alcohol, $C_{18}H_{37}OH$. These alcohols are used as emulsifying agents, as bases for pharmaceutical preparations, and in making detergents (p. 213). They are manufactured by methods to be described later.

Chemical Properties of the Alcohols. The characteristic grouping of the alcohols is the hydroxyl group. We have already seen that this group in ethyl alcohol can react in two different ways (equations 1b and 2b, p. 4). The hydrogen atom attached to oxygen may be replaced, as in the formation of **sodium ethoxide** (C_2H_5ONa), by the action of metallic sodium. This is a general reaction of alcohols; metallic potassium reacts in the same manner as sodium, and aluminum and magnesium react similarly in the presence of a very small amount of mercury. The resulting compounds, which are obtained as colorless crystalline solids by boiling off the excess alcohol, are known as *alkoxides*. The student will readily recognize that in this reaction the alcohols resemble the inorganic acids by having a hydrogen replaceable by metals. However, the common metals such as zinc and iron,

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which will react with acids, are without effect on alcohols; furthermore, alcohols in water solution are not neutralized by bases; instead the compound C_2H_5ONa is completely hydrolyzed by water, forming alcohol and sodium hydroxide.

$$C_2H_5ONa + H_2O \longrightarrow C_2H_5OH + NaOH$$

For these reasons we do not usually regard alcohols as acids.

The alkoxides form an important and useful group of derivatives of the alcohols. They are the organic equivalents of the strong inorganic bases, sodium or potassium hydroxide, and they can be used as such in organic solvents. Besides this general use, the student will encounter special uses from time to time (see p. 134). Sodium methoxide and several of the aluminum alkoxides are now available commercially.

The interaction of phosphorus trichloride and ethyl alcohol illustrates a second type of reaction in which the whole *hydroxyl group* is replaced. We shall consider in the next chapter a number of reactions of the alcohols which lead to the production of many interesting and important substances. All these reactions fall into one of two classes; either the hydrogen atom of the hydroxyl group is involved or the entire hydroxyl group is replaced by another atom or group. These replacement reactions are characteristic of all the compounds $C_nH_{2n+1}OH$ irrespective of whether they are primary, secondary, or tertiary alcohols.

The lower members of the alcohol series resemble water, as might be expected from the presence of an hydroxyl group. With the increase of the number of carbon atoms in the molecule, the influence of the hydroxyl group becomes less pronounced and the similarity to water becomes less evident. This is clearly seen in the progressive decrease in the solubility in water of the alcohols above propyl. Another illustration of the same principle is seen in the fact that methyl and ethyl alcohol combine with a number of inorganic salts such as calcium chloride forming crystalline compounds containing *alcohol of crystallization;* for example, $CaCl_2 \cdot 4C_2H_5OH$; $MgCl_2 \cdot 6CH_3OH$. The analogy between alcohol of crystallization and water of crystallization is evident. The higher alcohols do not combine with inorganic salts in this manner.

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QUESTIONS AND PROBLEMS

1. Define and illustrate the following terms: *structural formula*, *empirical formula*, and *molecular formula*.

2. Write balanced equations for the reactions between phosphorus trichloride and each of the following alcohols: isopropyl alcohol, methyl-propyl-carbinol, and isobutyl alcohol.

3. Write structural formulas for all of the amyl alcohols.

4. What is absolute alcohol, and how is it prepared?

5. When an alcohol reacted with excess potassium the hydrogen evolved by 1.80 g of the alcohol had a volume of 336 ml at standard conditions. What is the molecular weight of the alcohol?

6. Name each of the following alcohols: $CH_3CHOHCH(CH_3)_2$, $(CH_3)_3CCH_2OH$, $CH_3CH_2CHOHCH_2CH_2CH_3$, $CH_3CH_2CH_2CH_2CH_2OH$,

$$\begin{matrix} CH_3CH_2 \\ \qquad\quad \diagdown \\ \qquad\quad\ CHCHOHCH_3. \\ \qquad\quad \diagup \\ CH_3 \end{matrix}$$

7. How are the alkoxides prepared, and what are their uses?

8. Define and illustrate the terms *isomerism* and *homologous series*.

9. Do the following pairs of formulas represent the same or different substances:

a. $CH_3CH_2CH_2CHOHCH_3$ and $CH_3CH_2CHOHCH_2CH_3$

b. $CH_3CH_2CH_2CH_2CH_2OH$ and $HOCH_2CH_2CH_2CH_2CH_3$

10. How much methyl alcohol would it be necessary to add to the water in an automobile radiator to protect against freezing to $-10°$? You may assume that the volume of liquid in the cooling system is 10 l, and that when 100 ml of methyl alcohol is mixed with 100 ml of water the volume of the resulting solution is 200 ml. Could you use normal butyl alcohol instead of methyl alcohol?

11. Write balanced equations for the reactions between:

a. magnesium and methyl alcohol

b. potassium and *tert.*-butyl alcohol

c. aluminum and ethyl alcohol

12. Calculate the percentage composition of: (*a*) C_3H_6, (*b*) C_6H_6O, (*c*) C_5H_5N, (*d*) $C_7H_{10}NBr$.

13. Calculate the empirical formulas of the substances which gave the following percentages of the elements on analysis: (*a*) C, 62.80; H, 6.70; (*b*) C, 67.38; H, 3.75; N, 7.49; (*c*) C, 75.81; H, 3.73; N, 3.05; (*d*) C, 72.9; H, 4.71; (*e*) C, 69.12; H, 4.19; Cl, 11.35. (*Hint:* The percentage of oxygen is obtained by difference. The absence of elements other than those stated is assumed.)

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14. Classify the following alcohols according to whether they are primary, secondary, or tertiary: $(CH_3)_3CCH_2CH_2CH_2CH_2OH$, $CH_3CH_2CHOHCH_3$, $(CH_3)_3COH$, $(CH_3)_2CHCH_2OH$.

15. One liter of a gaseous compound, whose elementary analysis is C, 24.25; H, 4.05; Cl, 71.80, weighs 3.14 g at 760 mm and 110°. What is the molecular formula?

16. An alcohol on analysis was found to contain 64.9 per cent carbon and 13.5 per cent hydrogen. One gram of the substance reacted with metallic potassium to evolve 169 ml of hydrogen at 780 mm and 25°. What is the molecular formula of the substance?

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Chapter 2

ALKYL HALIDES AND ETHERS

In this chapter we shall continue our study of the alcohols by examining in more detail some of their general reactions and the substances which can be prepared from them by these reactions. We have already seen that a substance C_2H_5Cl is formed by the interaction of phosphorus trichloride and ethyl alcohol. It is a representative of one of the most important classes of organic compounds, the *alkyl halides.* Since they are readily prepared from the alcohols and in turn can be transformed into many compounds, we shall find that the alkyl halides are of great value to the chemist.

ALKYL HALIDES

The alkyl halides are compounds in which the hydroxyl group of an alcohol has been replaced by a halogen atom. For example, **methyl chloride,** CH_3Cl, may be prepared from methyl alcohol, CH_3OH, or **ethyl chloride,** C_2H_5Cl, from ethyl alcohol, C_2H_5OH. If we let **R** represent any alkyl group, **ROH** is an alcohol and **RCl** an alkyl chloride.

Preparation of Alkyl Halides. Alkyl chlorides, bromides, and iodides are readily prepared by either of two methods. These may be illustrated by the equations for preparing ethyl iodide.

$$1.\ C_2H_5OH + HI \xrightarrow{\text{Distill}} C_2H_5I + H_2O$$
$$2.\ 3C_2H_5OH + P + 3I \longrightarrow 3C_2H_5I + P(OH)_3$$

Both methods can be used with any simple alcohol. The second is commonly employed for preparing iodides; the iodine and phosphorus first react, forming phosphorus triiodide, this then reacts with the alcohol. Similarly, if one uses phosphorus tribromide or phosphorus trichloride instead of a mixture of phosphorus and iodine, the corresponding bromide and chloride can be prepared. Indeed, this is

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the reaction we first used to prove that ethyl alcohol contained an hydroxyl group.

Physical Properties. The properties of certain of the alkyl halides are tabulated below. It is convenient to remember that the simplest chloride which is a liquid at room temperature is the propyl compound, the simplest bromide the ethyl compound, and that methyl iodide is the only methyl halide which is not a gas under ordinary conditions. The general effect on the boiling point of increasing the molecular weight is well illustrated by the alkyl halides. The alkyl halides are all practically insoluble in water, and the bromides and iodides have a density greater than one.

REPRESENTATIVE ALKYL HALIDES

Name	*Formula*	*Boiling Point*	*Density at 20°*
	Chlorides		
Methyl chloride	CH_3Cl	−24°	0.991 (at −24°)
Ethyl chloride	CH_3CH_2Cl	+12°	0.910
n-Propyl chloride	$CH_3CH_2CH_2Cl$	47°	0.890
Isopropyl chloride	$CH_3CHClCH_3$	37°	0.860
	Bromides		
Methyl bromide	CH_3Br	+ 5°	1.732 (at 0°)
Ethyl bromide	CH_3CH_2Br	38°	1.430
n-Propyl bromide	$CH_3CH_2CH_2Br$	71°	1.353
Isopropyl bromide	$CH_3CHBrCH_3$	60°	1.310
	Iodides		
Methyl iodide	CH_3I	+43°	2.279
Ethyl iodide	CH_3CH_2I	72°	1.933
n-Propyl iodide	$CH_3CH_2CH_2I$	102°	1.747
Isopropyl iodide	CH_3CHICH_3	90°	1.703

Ionic and Covalent Bonds. Polar and Nonpolar Compounds. A comparison of the alkyl halides with the halides of the alkali metals will bring out a distinction that is essential to an understanding of organic chemistry. The student will certainly have encountered earlier in his study of chemistry the distinction between a **covalent linkage** or bond and an **electrovalent linkage** or bond: in a covalence two electrons are shared between two atoms; in an electrovalence one electron is transferred from one atom to another and electrostatic charges on the atoms result. In the alkyl halides we have covalences; in the alkali halides, electrovalences.

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Ionic Bond	$Na^+ \; :\ddot{\underset{\cdot\cdot}{Cl}}:^-$	Complete transfer of one electron. Ions independent and move freely in the molten salt or in solutions; held in rigid crystal lattice in the solid. Molecules in the gas (above *ca.* 1500°) held together by electrostatic force.
Covalent Bond	$\begin{array}{c} H \\ \cdot\cdot \quad \cdot\cdot \\ H:C:Cl: \\ \cdot\cdot \quad \cdot\cdot \\ H \end{array}$	No charge on any atom. Two electrons shared between carbon and chlorine, as between carbon and hydrogen. Four covalent bonds; no ions.

These two different types of linkages are reflected in the different properties and behavior of the compounds in which they occur. In their physical properties we have the following contrasts.

Alkyl Halides e.g., CH_3Cl	Alkali Halides e.g., NaCl
Low-boiling liquids; boiling points increase regularly with increasing molecular weight.	High-melting solids; vaporized only at extremely high temperatures.
Nonconductors of electricity.	Conduct electricity with electrolytic decomposition in the molten state or in solution.
Soluble in nonpolar solvents. Insoluble in water.	Soluble in water. Insoluble in nonpolar solvents.

In their reactions we have the equally striking contrast that the polar compounds in solution react practically instantaneously and show the reactions characteristic of the ions involved; while the nonpolar compounds require appreciable time for reaction, and each compound differs slightly in its behavior from the others.

Most molecules are neither so extremely polar or nonpolar as the examples just cited. And some molecules are so nicely balanced that their character depends upon the environment. Most organic compounds, however, are essentially nonpolar, with the result that low melting and boiling points, solubility in organic solvents, and appreciable reaction times are the rule in organic chemistry. The exceptions to the rule will be noted as they are encountered.

Hydrogen chloride is illustrative of the molecule whose character depends on its environment. In the liquid or gaseous states hydrogen

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chloride behaves as if the bond joining the hydrogen and chlorine atoms were entirely covalent. The substance is volatile and a poor conductor of electricity. So it is also in solvents with which it does not react and which have a low dielectric constant. In water, however, hydrogen chloride is a strong acid and is considered to be made up of chloride ions and hydrated hydrogen ions.

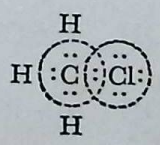
Electronic Theory of Valence. The difference in physical properties and chemical behavior of the alkyl halides and the halides of the alkali metals is explained very satisfactorily by the electronic theory of valence. This theory, which has been developed in the last twenty-five years, now stands on as firm ground as did the atomic theory seventy-five years ago. The student would do well to review the elements of this theory which are given in modern elementary books on inorganic chemistry. Here we may summarize for convenience that portion of the theory which is of particular significance to the study of organic chemistry.

Each atom is composed of a dense nucleus and a surrounding group of electrons which it is convenient to think of as arranged in shells. In the electrically neutral atom the positive charge on the nucleus is numerically equal to the total number of surrounding electrons. Only the electrons in the outermost shell of the common elements are concerned in chemical reactions. Therefore it is not the total number of electrons around an atom that is worth remembering, but the normal number in the outer shell. For the elements commonly met with in organic chemistry, the numbers are as follows.

Hydrogen	Carbon	Nitrogen	Oxygen	Sulfur	The Halogens
H	C	N	O	S	X
1	4	5	6	6	7

(The halogens, Cl, Br, I, are here represented by the symbol X, a convention often used in organic chemistry. Fluorine is not included in this summary formulation, for, as we shall see, the alkali fluorides are rather unlike the chlorides, bromides, and iodides.)

When an ionic or electrovalent bond is established there is a complete transfer of an electron from one atom to another as in sodium chloride. The reason why such a transfer takes place seems to be closely connected with the great stability of a grouping of eight electrons (an octet) in the outer shell of the many nonmetallic elements. This same arrangement of electrons can also be achieved, however, by the sharing of electrons, as in the covalent bond of two electrons. Thus in methyl chloride the carbon and chlorine atoms can both be considered to have complete octets if we count in both octets the two electrons shared by carbon and chlorine, and if we count the hydrogen-carbon bond electrons also as part of the carbon octet. In the following diagram each octet is circumscribed by a dotted line; it will be seen that the octets interpenetrate.



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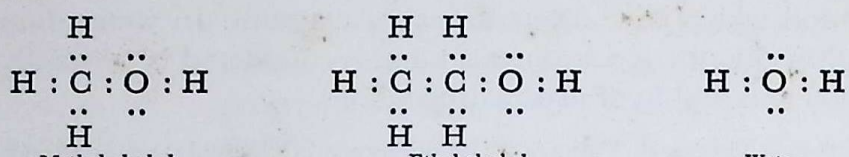
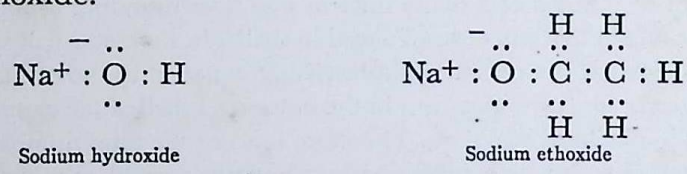
Electronic Formulas of Alcohols. We are now in a position to write electronic formulas also for the compounds discussed in Chap. 1, the alcohols.



Methyl alcohol — Ethyl alcohol — Water

The electronic formula for water is given for comparison.

The linkages in these three compounds are all covalences. However, by the replacement of the hydroxyl hydrogen atom by a metal such as sodium (p. 16) a substance is formed which has one ionic bond. Thus with water we have sodium hydroxide; with ethyl alcohol, sodium ethoxide.



Sodium hydroxide — Sodium ethoxide

In each compound we have a positive sodium ion and a negative ion in which the oxygen atom has a negative charge, namely the hydroxyl ion and the ethoxide ion.

The reason for the negative charge on oxygen is evident if we remember that the neutral oxygen atom has only six electrons in the outer shell. If we count the electrons in the above formulas we see that one electron in the oxygen octet has been obtained by transfer. Or, to put it another way, the oxygen has seven electrons, one more than its normal quota, and carries a negative charge.

Reactions of Alkyl Halides. The alkyl chlorides, bromides, and iodides enter into a number of characteristic reactions which are of great importance in organic chemistry. The halogen atom in an organic molecule usually represents a point of attack and can often be replaced by another atom or group. Several illustrations of this type of *metathetical reaction* are given below.

$$CH_3 \boxed{I + Na} CN \longrightarrow CH_3CN + NaI$$

$$CH_3 \boxed{I + Na} OCH_3 \longrightarrow CH_3OCH_3 + NaI$$

$$CH_3 \boxed{I + Ag} OH \longrightarrow CH_3OH + AgI$$

$$R \boxed{X + Ag} OH \longrightarrow ROH + AgX$$

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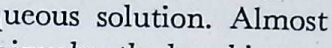
In all such metathetical reactions the iodides react most rapidly, the chlorides least rapidly, the bromides occupying an intermediate position.

Another metathetical reaction of alkyl halides is the replacement of one halogen atom by another. This is carried out by heating an alkyl halide with an inorganic halide in an anhydrous solvent (anhydrous acetone and lithium or potassium halides are often employed).



$$C_2H_5Br + KI \longrightarrow C_2H_5I + KBr$$

Variations in Rates of Reaction. Reactions involving covalent bonds are obviously very different from the ionic reactions with which the student is familiar from his study of the behavior of simple inorganic salts in aqueous solution. Almost all the transformations of organic chemistry involve the breaking and making of covalent bonds: as examples, the four metathetical reactions of the alkyl halides just given may be mentioned. Such reactions, unlike ionic reactions, take an appreciable time for completion. The speed or rate of the reactions usually varies enormously with changes in the experimental conditions. The factors affecting the rate of reaction of a given substance are in general: (1) concentration of the reacting substance (in the gas phase, pressure), (2) temperature, (3) solvent, (4) catalysts. To attempt to give the exact or quantitative relation between the rates of each type of reaction and these variables is beyond the province of this book. In a general or qualitative sense, the following rules are valid: the rates of most organic reactions are increased by increasing the concentration of both reactants, by increasing the temperature, and by the presence of small amounts of materials known as *catalysts*.

If one of the reactants is a polar substance (as in the metathetical reactions given on page 24), its solubility in the nonpolar organic compound is very low. Therefore a solvent which will dissolve both reactants is employed. This increases the concentration of the polar substance very greatly. Ethyl alcohol is frequently employed for this purpose as most nonpolar substances of low molecular weight are very soluble in it, and even polar substances are slightly soluble. It is thus common practice to use ethyl alcohol in the reaction between sodium cyanide and an alkyl halide. Where no solvent can be found, as in the reaction involving silver hydroxide, the solid is used in as fine a state of subdivision as can be achieved. The size of the particles and the way the material is prepared have profound effects on the rate.

Obviously one wants a reaction to proceed as rapidly as possible

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in the laboratory or in industry (provided it does not go with explosive speed!), therefore it is usual to operate at a temperature at which the reaction is nearly complete in a few hours. **In general, raising the temperature 10° doubles the rate of an organic reaction.** In the laboratory the boiling point of the reactants or the solvent conveniently determines the temperature when a return or reflux condenser is employed. If one of the reactants is a gas or a very volatile liquid, however, for example, ethyl chloride, temperatures above room temperature can be obtained only under pressure. In such cases the reaction mixture is placed in a tightly closed metal cylinder known as an *autoclave* (Fig. 16, p. 444). These autoclaves are of many sizes for use in the laboratory or in industry. They are built to stand high pressures and are often equipped for heating electrically or by steam under pressure.

As a reaction proceeds toward completion the rate diminishes because the concentrations of the reactants fall off as they are used up. If one substance is much more valuable than another it is common practice to use a large excess (two- or threefold, perhaps) of the cheaper reactant; under these conditions only the concentration of the other reactant diminishes toward the end and the speed does not fall off so rapidly. As the student soon learns from his experience in the laboratory, very few reactions in organic chemistry ever are quantitative; that is, go to 100 per cent completion. Not only would it take a very long time to use up the last fraction of a per cent of initial material, but side reactions leading to other products almost always occur. Indeed, it is to avoid these competing side reactions and thus obtain the maximum yield of the desired product, that the chemist in the laboratory seeks to find the most advantageous combination of temperature, solvent, concentration of reactants, and catalysts. Herein lies the art of organic chemistry as a laboratory science.

Effect of Structure on Reaction Rates. As already stated, in the metathetical reactions of the alkyl halides the iodides react more rapidly than the bromides, which in turn react more rapidly than the chlorides. The methyl halides react somewhat more rapidly than the derivatives of the higher normal alcohols, but the differences are not great. On the other hand the rates of reaction of the halides derived from secondary and tertiary alcohols are often markedly different from those of the primary compounds. For example, in the interaction with an alkali metal iodide (e.g., sodium iodide) tertiary butyl chloride requires about fifty times longer than does normal butyl chloride for the reaction to reach a given point; in general the secondary halides lie in between such extremes.

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Reaction between Alcohols and Halogen Acids. While the rates of the metathetical reactions of the halides of isomeric alcohols are in the order primary > secondary > tertiary, the speed of formation of the halides from the alcohol and an acid is just the opposite. Tertiary butyl alcohol, for example, when mixed with concentrated hydrochloric acid at room temperature forms tertiary butyl chloride in a few minutes. Normal butyl alcohol in the same reaction, however, reacts so slowly that zinc chloride must be used as a catalyst to give an appreciable yield in a practical period of time. It should be pointed out in this connection that, with those alcohols which are slightly soluble in water, aqueous acids cannot be used. Instead the alcohol is saturated with dry hydrogen halide gas. The speed of the reaction under these conditions is in the following decreasing order: HI > HBr > HCl.

Significance of Conditions. When we write the equation for a reaction in organic chemistry we should note the special conditions over the arrow. If no special conditions are noted we mean that the reaction takes place at a convenient rate in a common solvent at temperatures between about 20 and 100°. Always bearing in mind that variations in rates of reactions are the rule, we shall not emphasize variations in rates or special conditions of solvent, temperature, or catalysts in this book unless the variations are so great as to make the reaction in question a special one. We shall have many occasions, however, to direct the reader's attention to such special conditions.

It has become accepted usage to say that a reaction "does not go" at a certain temperature, but "takes place" at another, and higher, temperature. Such phrases often lead to confusion. Unless otherwise specified we mean by statements of this sort that below a certain temperature range the reaction in question goes so slowly as to be immeasurable, while above this temperature range it proceeds at a convenient rate. The critical temperature is often recorded as though it were as definite as a boiling point, but in fact it represents always a narrow critical range rather than a point.

The Grignard Reagent. A special reaction of the alkyl halides is of so much importance in the synthesis of organic compounds as to deserve individual attention. This reaction was discovered by the French chemist Victor Grignard.[1] In recognition of the discovery he

[1] Victor Grignard (1871–1935). Professor at the Chemical Institute of Lyons, France.

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was awarded one-half the Nobel Prize for the year 1912. The equations are:

$$CH_3I + Mg \xrightarrow[\text{ether}]{\text{Dry}} \underset{\text{Methylmagnesium iodide}}{CH_3MgI}$$

$$RX + Mg \xrightarrow[\text{ether}]{\text{Dry}} RMgX$$

Compounds of the type RMgX are called *Grignard reagents;* they are prepared and used in ether solution. They react with water violently at room temperature; this reaction enables us to prepare a type of substance known as a *hydrocarbon* which we are going to discuss in detail in the next chapter. The reaction between a Grignard reagent and water may be illustrated using methylmagnesium iodide.

$$CH_3MgI + H_2O \longrightarrow \underset{\text{Methane}}{CH_4} + Mg\begin{matrix} OH \\ I \end{matrix}$$

$$RMgX + H_2O \longrightarrow \underset{\text{Hydrocarbon}}{RH} + Mg\begin{matrix} OH \\ X \end{matrix}$$

(For convenience we write $Mg\begin{matrix} OH \\ X \end{matrix}$ to represent a mixture of $Mg(OH)_2$ and MgX_2.)

In a similar manner methylmagnesium iodide will form methane when treated with acids, alcohols, ammonia, and many other substances which have a so-called active hydrogen atom, usually hydrogen attached to some element other than carbon. This is illustrated by the following diagram:

$$\begin{matrix} CH_3 & \vdots & MgI \\ H & \vdots & OH \\ H & \vdots & OC_2H_5 \\ H & \vdots & Br \\ H & \vdots & NH_2 \end{matrix}$$

Since the product, methane, is a gas it can be conveniently collected and measured, and the amount of "active hydrogen" in a given weight of material may thus be estimated.

Other reactions of the Grignard reagent are used in the preparation of organic compounds; these will be discussed in later chapters.

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Other Metallic Alkyls. A large number of organometallic compounds which are prepared directly or indirectly from alkyl halides are known. Of these we shall mention a few.

Lithium alkyls can be prepared from alkyl halides and lithium in the presence of ether.

$$RX + 2Li \xrightarrow[\text{ether}]{\text{Dry}} RLi + LiX$$

They have found use where magnesium reacts very sluggishly with the alkyl halide. In general, lithium alkyls behave as the Grignard reagent in chemical reactions.

Zinc alkyls can be made from alkyl halides and zinc coated with copper, in the presence of a small quantity of ethyl acetate.

$$CH_3I + Zn \longrightarrow CH_3ZnI$$

For the most part they are similar to the Grignard reagent in their reactions, and are used only for a few special reactions. Like the Grignard reagent, zinc alkyls on distillation give a metallic dialkyl, ZnR_2.

$$2CH_3ZnI \longrightarrow (CH_3)_2Zn + ZnI_2$$

The zinc alkyls are spontaneously inflammable in air, and the preparation must therefore be carried out in an inert gas such as hydrogen or nitrogen. They were first prepared by Frankland[1] and, before the discovery of the Grignard reagent, were frequently used in the preparation of organic substances in the laboratory. Now they are almost entirely displaced by the Grignard reagent.

Lead tetraethyl produced commercially in large amounts (about 10 thousand tons annually) for the gasoline industry (p. 108) is prepared from ethyl chloride and one of the alloys of lead and sodium.

$$4C_2H_5Cl + 4NaPb \longrightarrow (C_2H_5)_4Pb + 4NaCl + 3Pb$$

It is a highly toxic liquid, soluble in organic solvents and boils at 202° C.

Alkyl Fluorides. Just as the element fluorine differs considerably from the other members of the halogen family, so the alkyl fluorides are compounds which have but little in common with the alkyl chlorides, bromides, and iodides. They are usually prepared by a special reaction—the interaction of an inorganic fluoride and an alkyl halide—

[1] Edward Frankland (1825–1899). An English chemist whose work laid the foundations of the theory of valence.

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though they may be formed by heating an alcohol with hydrofluoric acid. The lower alkyl fluorides are gases; propyl fluoride boils at −2°, *n*-amyl fluoride at 63°. Unlike the chlorides, bromides, and iodides the halogen atom in the fluorides is very unreactive. Methyl fluoride reacts but very slowly with even strong sodium hydroxide or sodium ethoxide.

Industrial Uses of the Alkyl Halides. The alkyl halides find extensive use for the introduction of alkyl groups in the manufacture of fine chemicals, but only a few alkyl halides are themselves heavy tonnage chemicals. Ethyl chloride, as has already been mentioned, is used in the manufacture of tetraethyl lead. Methyl chloride is employed for the dispersal of insecticides: the chloride, liquefied under pressure, volatilizes when the pressure is released and disperses the insecticide in extremely fine droplets. Methyl bromide is used as a fumigant.

ETHERS

Another important class of substances which are prepared directly from the alcohols are the ethers. The nature of these compounds will be best understood by studying the commonest representative, diethyl ether, usually called simply *ether*. It has been an important substance for nearly a hundred years; without this anesthetic modern surgery might never have developed.

Preparation of Ethyl Ether. Ether is readily prepared from ethyl alcohol by heating this substance with sulfuric acid. The following reactions take place:

$$C_2H_5OH + H_2SO_4 \longrightarrow \underset{\text{Ethyl sulfuric acid}}{C_2H_5OSO_3H} + H_2O$$

$$C_2H_5OSO_3H + C_2H_5OH \xrightarrow{130°-140°} CH_3CH_2OCH_2CH_3 + H_2SO_4$$

The preparation of ether from alcohol by this method is one of the oldest known organic reactions and is still the commercial process. Ether was manufactured in this way long before the nature of the reaction had been discovered. The alcohol is allowed to flow into a mixture of alcohol and sulfuric acid heated to 130° to 140°; ether and some alcohol and water distill and are condensed. The equations written above show that there are really two steps in the process: in the first, ethyl sulfuric acid is formed by interaction of ethyl alcohol and sulfuric acid; in the second, this substance reacts with more alcohol forming ether and regenerating sulfuric acid. The regenerated

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acid then reacts with more alcohol forming ethyl sulfuric acid (first reaction). At first sight it would appear that a given amount of sulfuric acid could thus convert an unlimited amount of alcohol into ether. Actually this is not so in the laboratory because, as the sulfuric acid becomes more dilute, water and alcohol distill with the ether and the process becomes too inefficient.

The temperature of the reaction mixture must be controlled rather carefully. At temperatures below 130°, the second reaction is so slow

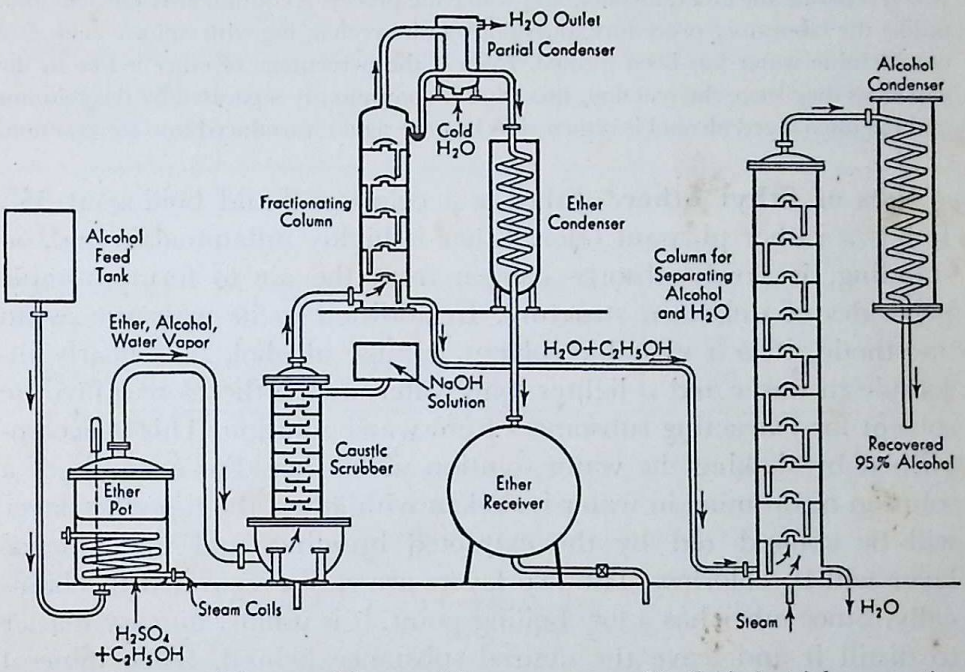

FIG. 2. Diagram of the essential parts of the apparatus used in the industrial preparation of ether. (From data kindly furnished by E. B. Badger and Sons Co.)

that unchanged alcohol will distill; at high temperatures (150° to 200°), ethyl sulfuric acid decomposes (p. 53). This is an excellent illustration of the principle mentioned earlier, namely, that the *conditions are of supreme importance in determining the course of an organic reaction.* In this case, a relatively slight change in the temperature greatly alters the efficiency of the process.

Industrial Apparatus for Preparing Ether. The industrial preparation of ether is illustrated by the diagram shown in Fig. 2. This is a simplified representation of the modern equipment which permits the production of an almost unlimited amount of ether from one charge of acid. The operation is as follows. The ether pot is charged with pure concentrated sulfuric acid; ethyl alcohol is then added and the mixture allowed to stand for some time during which ethyl sulfuric acid is formed (reaction 1, p. 30). The pot is then heated by passing steam through the coils which are below the

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level of the liquid. The temperature is kept at 130°, and alcohol is slowly run in from the alcohol feed tank. The vapor which issues from the ether pot contains alcohol, water, ether, and a small amount of acid fumes (sulfur dioxide). The latter are removed by contact with sodium hydroxide in the caustic scrubber. The vapors then pass through a series of complicated fractionating columns and partial condensers which separate the ether from the alcohol and water. The water and alcohol are separated in another column, and 95 per cent alcohol recovered. The temperatures of the ether pot and the various fractionating columns are carefully regulated. The process may be run continuously for many weeks. Because of the fractionating columns which separate the ether, alcohol, and water the process is continuously efficient and, unlike the laboratory procedure, does not require recharging with sulfuric acid after considerable water has been formed. Even if the percentage of ether is low in the vapors as they leave the reaction, this ether is continuously separated by the columns and the unchanged alcohol is returned to be once again introduced into the reaction.

Uses of Ethyl Ether. Ether is a colorless liquid boiling at 35°. It has a rather pleasant odor. Ether is highly inflammable, and, on standing, it slowly absorbs oxygen from the air to form unstable peroxides of unknown structure. In addition to its wide use as an anesthetic, it is a valuable solvent. Unlike alcohol, it is nearly insoluble in water and is lighter than water, and is therefore a favorite solvent for extracting substances from water solution. This is accomplished by shaking the water solution with ether. For example, if a solution of bromine in water is shaken with ether, the top ether layer will be colored red by the extracted bromine, and the aqueous layer will be colorless. The two layers are easily separated mechanically. Since ether has a low boiling point, it is usually an easy matter to distill it and leave the desired substance behind. Salts, mineral acids, and bases do not pass into an ether layer under such a treatment, but almost all organic substances, except salts and polyhydroxy compounds, are extracted to some extent. By repeating the process, many times if necessary, the organic material can be obtained in the ether layer. Extraction with ether is much used in the laboratory and in industry for the separation of organic from inorganic material.

Ether is often used as a solvent in which two substances are allowed to interact. Frequently for such purposes the ether must be free from water and alcohol, as in the preparation of Grignard reagents. Such **absolute ether** is made by treating ordinary ether with anhydrous calcium chloride, and then distilling from metallic sodium or phosphorus pentoxide.

Homologous Series of Ethers. The **homologous** series of ethers starts with methyl ether, the gas which is isomeric with ethyl alcohol;

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the first four members are given below. The lower members of this series are prepared either by the interaction of sulfuric acid and the alcohol in question at an elevated temperature, or by passing the vapors of a primary alcohol through a tube heated to 260° and containing alumina (Al_2O_3).

$$2ROH \xrightarrow[260^\circ]{Al_2O_3} ROR + H_2O$$

HOMOLOGOUS SERIES OF ETHERS

Name	*Formula*	*Boiling Point*	*Density at 20°*	*Solubility Grams per 100 Grams of Water*
Methyl ether	CH_3OCH_3	− 25°	—	1 vol of water dissolves 37 vols of gas
Ethyl ether	$CH_3CH_2OCH_2CH_3$	+ 35°	0.714	7.0
Propyl ether	$(CH_3CH_2CH_2)_2O$	+ 91°	0.746 (at 19°)	6.0
Butyl ether	$(CH_3CH_2CH_2CH_2)_2O$	+143°	0.768	—

Mixed Ethers. Ethers with two different groups are called *mixed ethers.* Such an ether is methyl ethyl ether. It cannot be prepared conveniently by the usual reaction, but instead is prepared by the Williamson[1] synthesis. The equations are as follows:

$$2C_2H_5OH + 2Na \longrightarrow \underset{\text{Sodium ethoxide}}{2C_2H_5ONa} + H_2$$

$$C_2H_5ONa + \underset{\text{Methyl iodide}}{CH_3I} \longrightarrow C_2H_5OCH_3 + NaI$$

Instead of methyl iodide, methyl sulfate may be used.

$$C_2H_5ONa + (CH_3)_2SO_4 \longrightarrow C_2H_5OCH_3 + CH_3OSO_3Na$$

Chemical Reactions of Ethers. Chemically, the ethers are noted for their inertness; they do not react with such reagents as metallic sodium, phosphorus trichloride, or alkalies. They are broken down into two molecules by warming with sulfuric acid or, more rapidly, with aqueous hydrogen iodide.

$$C_2H_5OCH_3 + 2HI \longrightarrow C_2H_5I + CH_3I + H_2O$$

This reaction is often used in determining the structure of ethers.

[1] First used by A. W. Williamson (1824–1904). Professor at University College, London.

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Ethers of Industrial Importance. Methyl ether is manufactured today by the catalytic dehydration of methanol. It finds use as a refrigerant since it can be allowed to come in direct contact with foodstuffs during "quick freezing" without imparting any foreign taste or odor. Isopropyl ether, $(CH_3)_2CHOCH(CH_3)_2$, (bp 68°) is commercially available, and in many industrial extraction processes it is beginning to replace ethyl ether. It is actually cheaper than ether, and because of its lower volatility it is less hazardous to handle. Higher ethers such as those obtained from the amyl alcohols are now produced. Their chief use is as solvents.

QUESTIONS AND PROBLEMS

1. Write electronic formulas for methyl bromide, potassium chloride, sodium hydroxide, and sodium ethoxide.

2. Write balanced equations for two methods of preparing (*a*) propyl chloride, (*b*) isopropyl bromide, and (*c*) ethyl iodide.

3. Arrange the three alkyl chlorides, *n*-butyl chloride, *sec.*-butyl chloride, and *tert.*-butyl chloride, in the order of increasing rate of reaction with sodium cyanide.

4. Name the following compounds: $CH_3CH_2OCH_2CH_2CH_3$, $CH_3CH_2CH_2CH_2MgCl$, $CH_3CHBrCH_3$, $(CH_3CH_2)_4Pb$, $NaOCH_2CH_2CH_3$, $CH_3CH_2CH_2CH_2Li$.

5. Write balanced equations for the reactions of *n*-butyl chloride and isopropyl bromide with sodium cyanide, sodium ethoxide, and silver hydroxide.

6. If 2 ml of a solution of methylmagnesium iodide on treatment with an excess of water evolves 1.568 ml of methane at standard conditions, what is the molarity of the Grignard reagent?

7. Name the following alcohols: $CH_3CH_2CH_2CH_2CH_2OH$, $CH_3CH_2CHOHCH_2CH_3$, $(CH_3)_2C(OH)C_2H_5$. Arrange these alcohols in the order of increasing rate of reaction with (*a*) hydrochloric acid and (*b*) sodium.

8. How does the electronic theory of valence account for covalences and electrovalences?

9. Write balanced equations for the formation of ethylmagnesium bromide, *n*-butyllithium, and isopropylmagnesium bromide and for their reaction with water.

10. What factors will affect the rate of the reaction between butyl bromide and (*a*) potassium iodide and (*b*) silver hydroxide?

11. Write balanced equations for two methods of preparing ethyl ether.

12. Compare the reactions of $C_2H_5OC_2H_5$ and $(CH_3)_3COH$ with the following reagents: sodium, phosphorus trichloride, hydrochloric acid, hydrogen iodide.

13. Why is it necessary to use absolute ether in the preparation of a Grignard reagent? How is absolute ether prepared in the laboratory?

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14. Assuming a 70 per cent yield in the reaction, how much butyl alcohol and hydrobromic acid would be required in order to prepare 100 g of butyl bromide?

15. If the reaction between butyl alcohol and hydrobromic acid to form butyl bromide runs to essential completion in 2 hours at 100°, approximately how long would be required at 20°?

16. A pure liquid isolated from a mixture of subtances was found to contain 64.86 per cent of carbon and 13.51 per cent of hydrogen. When it was added to a solution of ethylmagnesium bromide, no gas was evolved. A mixture of isopropyl and methyl iodides, however, was obtained by boiling the compound with hydriodic acid. What was the structure of the liquid?

17. By what simple chemical or physical tests could you differentiate between: (*a*) *n*-propyl alcohol and *n*-propyl ether; (*b*) lithium ethoxide and lithium ethyl; (*c*) *n*-amyl bromide and *n*-amyl alcohol?

18. List the general formulas for the types of compounds studied so far and include a few fundamental reactions of each.

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Chapter 3

SATURATED OR PARAFFIN HYDROCARBONS

In the last chapter we encountered compounds of the type RH (where R is an alkyl group) formed by the action of water on a Grignard reagent; these substances are known as *saturated hydrocarbons*. It will be clear from what has already been learned about the structure of alcohols and alkyl halides that the general formula of members of this class of compounds must be C_nH_{2n+2}. Another common name for the group is *paraffin hydrocarbons;* still another is the *alkanes*. We shall meet in the next chapter classes of substances also composed only of carbon and hydrogen, and hence called *hydrocarbons* but having less hydrogen than the paraffin series, and hence called *unsaturated hydrocarbons*.

The relationship between the compounds we have studied and the corresponding paraffin hydrocarbons is illustrated below.

Alcohol	*Alkyl Iodide*	*Hydrocarbon Alkane*	*Name of Hydrocarbon*
$C_nH_{2n+1}OH$ ROH	$C_nH_{2n+1}I$ RI	C_nH_{2n+2} RH	
CH_3OH	CH_3I	CH_4	Methane
CH_3CH_2OH	CH_3CH_2I	CH_3CH_3	Ethane
$CH_3CH_2CH_2OH$ $CH_3CHOHCH_3$	$CH_3CH_2CH_2I$ CH_3CHICH_3	$CH_3CH_2CH_3$	Propane

The alcohols and alkyl halides are often spoken of as *derivatives* of the paraffin hydrocarbons. A derivative of a hydrocarbon is a substance which might be prepared from the hydrocarbon by the replacement of a hydrogen atom by another atom or group. This is a purely formal relationship which is useful in classification. It does not state that the derivatives of the hydrocarbon are prepared in this way.

Isomerism in the Paraffin Series. It will be noticed that only one substance, propane, corresponds to both propyl and isopropyl alco-

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SOME NORMAL PARAFFIN HYDROCARBONS

Molecular Formula	*Name*	*Boiling Point*	*Melting Point*	*Density at 20°*
CH_4	Methane	−161°	−184°	—
C_2H_6	Ethane	− 88°	—	—
C_3H_8	Propane	− 45°	—	—
C_4H_{10}	*n*-Butane	+ 0.6°	—	0.601 at 0°
C_5H_{12}	*n*-Pentane	36°	−148°	0.631
C_6H_{14}	*n*-Hexane	69°	− 94°	0.658
C_7H_{16}	*n*-Heptane	98°	—	0.683
C_8H_{18}	*n*-Octane	126°	− 98°	0.702
C_9H_{20}	*n*-Nonane	150°	− 51°	0.719
$C_{10}H_{22}$	Decane	174°	− 32°	0.747
$C_{11}H_{24}$	Undecane	194.5°	− 26.5°	0.758
$C_{12}H_{26}$	Dodecane	214–216°	− 12°	0.768
$C_{13}H_{28}$	Tridecane	234°	− 6.2°	0.757
$C_{14}H_{30}$	Tetradecane	252.5°	5.5°	0.774 at mp
$C_{15}H_{32}$	Pentadecane	270.5°	10°	0.776 " "
$C_{16}H_{34}$	Hexadecane	287.5°	18°	0.775 " "
$C_{17}H_{36}$	Heptadecane	303°	22.5°	0.777 " "
$C_{18}H_{38}$	Octadecane	317°	28°	0.777 " "
$C_{19}H_{40}$	Nonadecane	330°	32°	0.777 " "
$C_{20}H_{42}$	Eicosane	205° (at 15 mm)	36.7°	0.778 " "

hols. Isomerism in the paraffin hydrocarbons is not met with until we come to the **butanes,** C_4H_{10}. There are two of these, normal or *n*-butane, $CH_3CH_2CH_2CH_3$, and isobutane, $\begin{matrix} CH_3 \\ CH_3 \end{matrix}\!\!>\!CHCH_3$; they boil at +0.6° and −10° respectively. The structural theory predicts three **pentanes,** C_5H_{12}, and three and only three such compounds are known. The student should satisfy himself that no arrangement of the atoms other than those shown below is possible.

ISOMERIC PENTANES (C_5H_{12})

Name	*Formula*	*Boiling Point*
n-Pentane	$CH_3CH_2CH_2CH_2CH_3$	36°
Dimethyl-ethyl-methane	$(CH_3)_2CHCH_2CH_3$	28°
Tetramethylmethane	$(CH_3)_4C$	10°

A rather complicated mathematical formula has been developed for calculating the number of possible isomers of a paraffin hydrocarbon. Application of this formula shows that the number of isomers increases with startling rapidity as we go up the

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series. Thus while there are only nine possible isomeric heptanes (all of which are known) there are 366,319 possible isomers with the formula $C_{20}H_{42}$. Calculation further shows that the number of isomeric hydrocarbons reaches 69,491,178,805,831 when we consider a paraffin hydrocarbon with forty carbon atoms! Needless to say only a very minute fraction of the total number of possible isomers of the hydrocarbons containing more than nine carbon atoms has been prepared.

Physical Properties. The lower members of the paraffin hydrocarbons are gases, the members above C_4H_{10} are liquids, and above $C_{16}H_{34}$ solids at room temperature. They are all insoluble in water.

FIG. 3. The boiling points of the normal paraffin hydrocarbons, CH_4 to $C_{19}H_{40}$.

The boiling points of the *straight-chain compounds* (called the *normal paraffin hydrocarbons*) are given in the table on p. 37 and are plotted in Fig. 3, above. The boiling points of the normal paraffins increase with increasing molecular weight just as do the boiling points of the alcohols; the rate of increase is greater with the lower members than with the higher (the curve becomes flatter). It is convenient to remember that *n*-pentane (C_5H_{12}) is the simplest member of the series that is liquid at ordinary temperatures. The highest straight-chain member of the series which has been so far prepared is heptacontane $C_{70}H_{142}$, a solid melting at 105°. The largest paraffin hydrocarbon so far synthesized, $C_{94}H_{190}$, has a molecular weight of 1318. It is a chain of seventy-six carbon atoms to which are attached eighteen methyl groups.

In general the straight-chain hydrocarbons have a higher melting point than the branched-chain compounds, and the melting point rises with increase in molecular weight. However, the melting point of a compound is determined by other factors

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than the molecular weight (for this reason, it is much more difficult to predict melting points than to predict boiling points). In particular the melting point of very symmetrical molecules is almost always surprisingly high. For example, the octane $(CH_3)_3CC(CH_3)_3$ is a crystalline solid at room temperature and melts at 103° to 104°, only a few degrees below its boiling point (106°); by contrast *n*-octane melts at −98°.

Nomenclature of Paraffins. The names of the simple members of the series follow the alcohols: for example, eth-yl alcohol, eth-ane. The five-carbon compound is an exception: instead of the expected "amane" the name *pentane* is used. From this point on, the number of carbon atoms is denoted by the prefix: thus, hexane, C_6H_{14}; heptane, C_7H_{16}; octane, C_8H_{18}; nonane, C_9H_{20}; decane, $C_{10}H_{22}$.

In naming complicated hydrocarbons, a system similar to that employed with the alcohols is often used. It will be recalled that methyl alcohol is considered as the parent substance; similarly, in naming the hydrocarbons, methane is chosen as a basis for the nomenclature. A convenient rule to remember is the following: *the most highly substituted carbon atom is considered the center of the molecule* and the alkyl groups attached to it are named. Thus

$$\begin{array}{l} CH_3 \\ \quad\diagdown \\ \quad\ \underline{C}HCH_2CH_3, \text{ dimethyl-ethyl-methane} \\ \quad\diagup \\ CH_3 \end{array}$$

$$(CH_3)_2CH\underline{C}(CH_3)_3, \text{ trimethyl-isopropyl-methane}$$

Here we have underlined the central carbon atom to illustrate the method of nomenclature. This is, of course, not usually done. It is advisable to practice writing and naming a variety of hydrocarbons to be certain that one is familiar with the principles employed.

The Geneva System of Nomenclature. The naming of complex substances presents many difficulties. Methods of naming simple substances are sufficient for the purposes of our elementary study of the subject, but they do not suffice when more complicated compounds are considered. In 1892 a congress of chemists adopted a systematic scheme of nomenclature. This system has become known as the *Geneva system*. The paraffin hydrocarbons are named according to the *longest continuous chain;* the name of the hydrocarbon with this number of carbon atoms is modified by noting what alkyl groups are attached to the chain. The chain is numbered and the positions of the substituent

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alkyl groups are indicated by numbers. For example, the hydrocarbon,

$$\overset{1}{CH_3}\overset{2}{C}\overset{3}{H}\overset{4}{CH_2}CH_3,\ \text{is 2-methylbutane;}\quad CH_3CH_2\overset{CH_3}{\overset{|}{C}}CH_2CH_2CH_3,\ \text{is 3,}$$
$$\quad\ \ |\qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad\ \ |$$
$$\quad CH_3\qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad\quad CH_3$$

$$\text{3-dimethylhexane, and } CH_3CH_2\overset{CH_3}{\overset{|}{C}H} - \overset{CH_2CH_3}{\overset{|}{C}H}CH_2CH_2CH_3 \text{ is 3-methyl-}$$

4-ethylheptane.

The alcohols of the series $C_nH_{2n+1}OH$ are named as derivatives of the hydrocarbons C_nH_{2n+2}. The terminal ending *-ol* is added to the name of the parent hydrocarbon, which is always considered as corresponding to the longest carbon chain carrying the hydroxyl group. The following examples illustrate the naming of alcohols by the Geneva system: $CH_3CHOHCH_2CH_3$ is butanol-2 (the 2 indicates the position of the hydroxyl group), $CH_3CHOH\overset{CH_3}{\overset{|}{C}H}CH_2CH_3$ is 3-methylpentanol-2. The alkyl halides are named by considering them as chloro, bromo, or iodo derivatives of the paraffin hydrocarbons and indicating the position of the halogen atom by a number; thus, isopropyl bromide, $CH_3CHBrCH_3$ is 2-bromopropane. The system includes all the many types of compounds which are known (e.g. unsaturated hydrocarbons, aldehydes, ketones, acids, cyclic compounds); a hydrocarbon is always considered as the parent substance and a characteristic ending of the name shows the reactive group.

Preparation of Paraffin Hydrocarbons. The preparation of the paraffin hydrocarbons from the corresponding alkyl halides by way of the Grignard reagent (p. 28) amounts to the replacement of a halogen atom by a hydrogen atom. Alkyl halides may also be converted into the corresponding hydrocarbon by direct reduction with "nascent hydrogen" generated by such combinations as zinc and acid, sodium and alcohol, or sodium amalgam and water.

$$C_2H_5Br + \underset{\text{"Nascent hydrogen"}}{2[H]} \longrightarrow C_2H_6 + HBr$$

The higher alkyl iodides may be reduced to hydrocarbons by heating with hydrogen iodide.

$$C_nH_{2n+1}I + HI \longrightarrow C_nH_{2n+2} + I_2$$

Higher members of the series may be prepared by joining two

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alkyl groups by the Wurtz[1] reaction in which metallic sodium reacts with an alkyl halide (or a mixture of two halides).

$$2CH_3 : I + 2Na : \longrightarrow \underset{\text{Ethane}}{CH_3CH_3} + 2NaI$$

$$CH_3I + 2Na + C_2H_5I \longrightarrow \underset{\text{Propane}}{CH_3CH_2CH_3} + 2NaI$$

If two different alkyl halides are employed there will be always two products besides the desired hydrocarbon. Thus in the example just given, some ethane, CH_3CH_3, and some butane, $CH_3CH_2CH_2CH_3$, will also be formed. The low yield of the desired product and the problem of separating it from the other two products limit the usefulness of the Wurtz reaction for joining together two unlike alkyl groups.

Hydrocarbons with fewer hydrogen atoms than the paraffins (unsaturated hydrocarbons) can often be prepared more readily than the saturated compounds. By the addition of further hydrogen (hydrogenation) they can be converted into the corresponding paraffin hydrocarbons. Examples of this will be given in later chapters, together with a consideration of reactions between saturated and unsaturated hydrocarbons which also yield paraffin hydrocarbons; these methods are nowadays the most important reactions for preparing individual members of the paraffin series in large quantities.

Petroleum and Gasoline. Petroleum is primarily a very complex mixture of hydrocarbons; small amounts of organic substances containing oxygen or nitrogen or sulfur are usually also present. The type of hydrocarbon which predominates seems to vary from one locality on the earth's surface to another. From the Pennsylvania and United States mid-continent petroleums the lower members of the paraffin series have been isolated in pure condition, but it is difficult to separate the very great numbers of isomers of the higher members. We shall reserve for a separate chapter the transformations of petroleum and the preparation of special gasolines now so important to the automotive and aviation industries. At that time we shall also consider the synthesis of gasoline and other organic compounds by the reduction of coal or carbon monoxide.

REACTIONS OF PARAFFIN HYDROCARBONS

Isomerization. In a great many of the transformations of organic compounds the structure of the hydrocarbon chain remains intact

[1] Adolph Wurtz (1817–1884). Professor at the École de Médecine, Paris.

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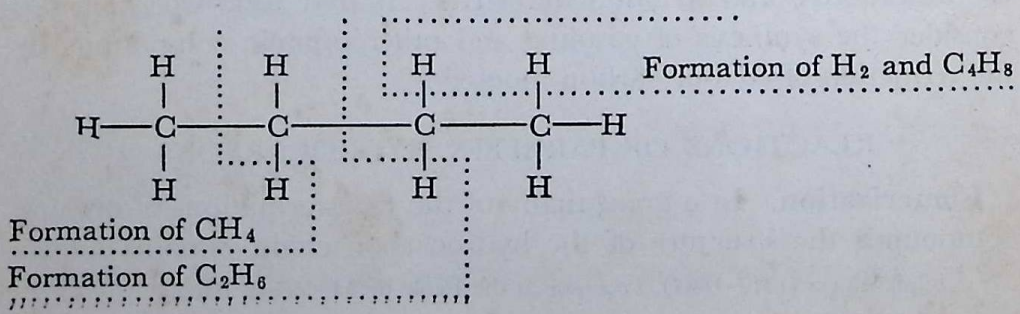
But there are reactions where this is not true and where one arrangement of carbon atoms is transformed into another. With the paraffin hydrocarbons such a reaction obviously involves the change of one isomer into another and is called *isomerization*. The reaction is brought about by a catalyst, aluminum chloride or aluminum bromide, and temperatures from 100° to 200° are commonly employed. The reaction usually does not go to completion but comes to an *equilibrium* position which can be approached from either side. Thus starting with either *n*-butane or isobutane and aluminum chloride or bromide one ends with a mixture of the two isomers. The percentage of the isomers in the final or equilibrium mixture depends on the temperature; the lower the temperature the larger the amount of the iso compound in the mixture.

$$CH_3CH_2CH_2CH_3 \underset{AlBr_3}{\overset{AlCl_3 \text{ or}}{\rightleftharpoons}} (CH_3)_3CH$$

Decomposition. The isomerization of hydrocarbons with five or more carbon atoms by means of catalysts and elevated temperatures is always complicated by another reaction which involves splitting the carbon chain. For example, when *n*-butane is kept in contact with aluminum chloride at about 100° for a considerable period of time one finds, in addition to the isomeric butanes, various hydrocarbons with fewer carbon atoms. Such decomposition reactions complicate the study of the other reactions of many of the higher paraffin hydrocarbons.

The decomposition reactions of the paraffin hydrocarbons may be illustrated by a few simple examples. When *n*-butane is passed through tubes kept somewhat above 400° the products are found to be hydrogen, methane, ethane, and four unsaturated hydrocarbons: ethylene, (C_2H_4); propylene, (C_3H_6); and two isomeric butylenes, (C_4H_{10}). These products can be considered as arising from the thermal decomposition of the butane molecule at the points indicated below:



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The removal of two hydrogen atoms which leaves the four carbon structure intact is known as *dehydrogenation;* the speed of this reaction can be enormously increased by the use of suitable catalysts. The reactions which occur at high temperatures and which involve the breaking of the carbon chain are called *thermal decomposition* reactions, *pyrolyses*, or *cracking reactions*. These reactions as well as dehydrogenation play a very important role in the modern petroleum industry (Chap. 6).

Replacement of Hydrogen by Halogen. Chlorine and bromine do not react with the paraffin hydrocarbons at an appreciable rate at room temperature under ordinary conditions. This fact is often taken advantage of in distinguishing between this group of hydrocarbons and the unsaturated hydrocarbons which, as we shall see in the next chapter, combine with bromine rapidly. At temperatures between 100° and 500° in hot tubes, and particularly in the presence of certain metallic salts as catalysts, **substitution reactions** occur. The illumination of the mixture by strong light, particularly ultraviolet light, has been found also to increase greatly the speed of such substitution reactions. In these reactions one or more hydrogen atoms are replaced by halogen (chlorine or bromine). Such reactions are called *halogenations;* if chlorine is used, *chlorination;* if bromine, *bromination*. Chlorination can also be effected by treatment of a hydrocarbon with sulfuryl chloride, SO_2Cl_2, in the presence of a peroxide. The reaction does not stop when one halogen atom has been introduced, but the resulting alkyl halide in turn enters into a substitution reaction. Thus a mixture of products is usually obtained. Furthermore, in all but the simplest compounds the possibility of forming isomeric products by substitution of hydrogen atoms on different carbon atoms is present so that complex mixtures are often obtained. For these reasons the halogenation of paraffin hydrocarbons is rarely employed in the laboratory, though certain industrial processes are based on this type of reaction. The interaction of methane and chlorine may be written as an illustration of the reaction.

$$CH_4 + Cl_2 \xrightarrow[\text{catalyst; high temperature}]{\text{Light or}} CH_3Cl \xrightarrow[\text{catalyst; high temperature}]{\text{Light or}} CH_2Cl_2 \xrightarrow[\text{catalyst; high temperature}]{\text{Light or}} CHCl_3 \xrightarrow[\text{Light or catalyst; high temperature}]{} CCl_4$$

Reaction with Nitric Acid. Nitration. One or more hydrogen atoms of the paraffin hydrocarbons can be replaced by the charac-

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teristic group of nitric acid, the nitro group $-NO_2$, by treatment of the paraffin hydrocarbon with nitric acid. The reaction can be carried out either in the gas phase, which is particularly suitable for hydrocarbons of low molecular weight; or by agitating the hydrocarbon with a mixture of concentrated sulfuric and nitric acids, which is particularly suitable for the hydrocarbons of higher molecular weight. The hydrogen atom on a tertiary carbon, that is, R_3CH, is replaced most readily; that on a secondary carbon, R_2CH_2, next; while the hydrogen atom of the CH_3 group is replaced at the slowest rate by the nitro group of nitric acid. The general reaction may be illustrated with pentane.

$$CH_3CH_2CH_2CH_2CH_3 + HNO_3 \xrightarrow{400^\circ} \begin{array}{l} CH_3CH_2\underset{\underset{NO_2}{|}}{C}HCH_2CH_3 \\ CH_3CH_2CH_2\underset{\underset{NO_2}{|}}{C}HCH_3 \\ CH_3CH_2CH_2CH_2CH_2NO_2 \end{array}$$

(And decomposition with formation of nitro compounds of lower hydrocarbons.)

PHYSICAL PROPERTIES OF SOME NITROPARAFFINS

Formula	*Name*	*Boiling Point*	*Melting Point*	*Density at 20°*
CH_3NO_2	Nitromethane	101°	−29°	1.139
$CH_3CH_2NO_2$	Nitroethane	114°	−90°	1.052
$CH_3CH_2CH_2NO_2$	1-Nitropropane	132°	−108°	1.003
$CH_3\underset{\underset{NO_2}{\vert}}{C}HCH_3$	2-Nitropropane	120°	−93°	0.992

A consideration of the electronic structure of the nitro group will be postponed until later. We need only note here that the carbon-nitrogen link is a covalent bond.

Oxidation. As compared with many classes of organic compounds the paraffin hydrocarbons are very resistant to oxidizing agents. For example, they are attacked only very slowly at room temperature by ozone (O_3), potassium permanganate ($KMnO_4$), potassium dichromate ($K_2Cr_2O_7$), or silver oxide (Ag_2O), reagents often used in organic chemistry. Compounds which contain a tertiary carbon atom and thus have the general formula R_3CH are often oxidized by potassium permanganate at room temperature, though not so rapidly as are the unsaturated hydrocarbons or the alcohols.

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The final products of the oxidation of all hydrocarbons are carbon dioxide and water. The interaction between atmospheric oxygen and the paraffin hydrocarbons when it proceeds at a high rate is the familiar phenomenon of **combustion.** There is usually a rather definite temperature above which a hydrocarbon in an excess of air is oxidized so rapidly that we say it *burns*. If the supply of air is insufficient but the temperature remains high, the products will contain carbon monoxide as well as carbon dioxide; with even less air elementary carbon will be produced. In this way *carbon black* and similar materials are prepared from natural gas which is a mixture of the lower paraffin hydrocarbons. The oxidation of paraffin hydrocarbons of larger molecular weight to useful products is described in Chap. 8.

Heats of Combustion. The amount of heat evolved when an organic compound is burned can be measured with accuracy in the laboratory. The number thus obtained, known as the *heat of combustion*, has value both from a practical and theoretical standpoint. Practically one is interested in knowing how much heat is involved in the combustion of a material if the substance in question is to be used as a fuel. In a later discussion of petroleum and gasoline we shall make use of the heats of combustion of hydrocarbons. The values of the heats of combustion to carbon dioxide and liquid water of some of the compounds we have already considered are listed below.

Molecular Formula	*Substance*	*Heat of Combustion of Material in Gaseous State (Kilogram calories per mole)*	*Difference between Members of the Series (Kilogram calories)*
CH_4	Methane	212.8	
C_2H_6	Ethane	372.8	160.0
C_3H_8	Propane	530.6	157.8
C_4H_{10}	*n*-Butane	688.0	157.4
C_4H_{10}	Isobutane	686.0	
C_5H_{12}	*n*-Pentane	845.0	157.0
CH_4O	Methyl alcohol	182.6	
C_2H_6O	Ethyl alcohol	336.8	154.2
C_3H_8O	Propyl alcohol	493.3	156.5
C_3H_8O	Isopropyl alcohol	489.5	
C_2H_6O	Dimethyl ether	347.6	
$C_4H_{10}O$	Diethyl ether	660.3	2(156.4)

Since it is very easy to use the wrong values in calculations involving the heat evolved in reactions, three points should be emphasized in

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regard to the figures given in the table: (1) the substance in question is in the gaseous state; (2) 1 mole of substance is involved; (3) these are the best averages of many experimental values, and the last figure is of doubtful significance. The heat of combustion of each of the materials in the liquid state is somewhat different. For example, for *n*-pentane the two values are gas 845.0, liquid 838.0; for *n*-decane, $C_{10}H_{22}$, gas 1630, liquid 1610.

The difference is obviously the heat of vaporization because in the gas that much more heat per mole is in the molecules and is liberated on combustion. The difference is small for compounds of low molecular weight but increases regularly with the number of carbon atoms since the heat of vaporization increases in the same way.

The regularity in the three series of compounds shown in the table is marked. For each increment of CH_2 in a straight chain about 157 kg-cal is added to the heat of combustion. This fact enables one to calculate the heats of combustion of simple compounds with a fair degree of accuracy. Abnormalities in the heats of combustion will be met with from time to time; they reflect special types of structure. Isomers, it will be noted, differ slightly one from another.

The formula for the calculation of the heats of combustion of the paraffin hydrocarbons is Heat of Combustion (kilogram-calories per mole of gas) $= 60.4 + 157n$, where n is the number of carbon atoms in the molecule. For the normal primary alcohols the corresponding formula is $21.6 + 157n$.

The heats of combustion generally used in chemistry are those measured at a constant pressure of 1 atm and 25°. The values for constant volume are slightly different if a volume change takes place during combustion and they have a somewhat different theoretical significance.

Exothermic Reactions. The heats of combustion just discussed are the heats evolved when the compounds are burned to carbon dioxide and liquid water. It is common practice to write the heat evolved or absorbed in a reaction on the right-hand side of the equation. Thus the combustion of gaseous methane may be written

$$CH_4 + 2O_2 \longrightarrow CO_2 + 2H_2O + 212.8 \text{ kg-cal}$$

Reactions in which heat is evolved are called *exothermic reactions*. A great many reactions in organic chemistry are of this type, but the amount of heat evolved varies greatly from reaction to reaction. Reactions where heat is absorbed (endothermic) are less common in organic chemistry, and when they do occur the amount of heat

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absorbed is always relatively small if the reaction runs to completion at room temperature.

A consideration of the heats of combustion of the two isomeric butanes and the isomerization of these compounds (p. 42) will illustrate the type of reaction which is weakly endothermic. Since *n*-butane is richer in energy (i.e., has a higher heat of combustion) by a few kilogram-calories than is the isomeric isobutane, the transformation of the latter into the former must involve a slight absorption of energy.

Calculation of Heats of Reaction. By simple inspection of the heats of combustion and the application of common-sense reasoning we can write the equation:

$$n\text{-butane} \longrightarrow \text{isobutane} + 1.7 \text{ kg-cal}$$

or the reverse

$$\text{isobutane} \longrightarrow n\text{-butane} - 1.7 \text{ kg-cal}$$

where the minus sign means heat absorbed; 1.7 kg-cal is said to be the heat of reaction. Where transformations other than isomerizations are concerned, the method of calculating the heat of the reaction is less obvious and more complicated. If we know the heats of combustion, however, of all the reactants and the products in an organic reaction we can calculate the heat of the reaction. Such heats we shall refer to from time to time without showing the methods of calculation.

QUESTIONS AND PROBLEMS

1. Name the following compounds: $CH_3CH_2CH(CH_3)CH_2CH_3$, $(CH_3)_2CHCHClCH_3$, $(CH_3)_2CHCH(CH_3)_2$, $CH_3CHOHCH_2CH_2C(CH_3)_3$, $CH_3CH_2CHBrCH_2CH_3$, $CH_3CH(CH_2CH_3)_2$, $(CH_3)_2CHC(CH_3)(C_2H_5)_2$.

2. Write balanced equations showing how you could prepare (*a*) *n*-butane and (*b*) *n*-octane from *n*-butyl bromide.

3. Write structural formulas and name all the isomeric hydrocarbons of the formula C_6H_{14}.

4. Which of the following hydrocarbons would react the more rapidly with nitric acid, and on what carbon atom would reaction first take place: $(CH_3CH_2)_2CHCH_3$ or $CH_3CH_2CH_2CH_2CH_3$?

5. What products would you expect to obtain by (*a*) treating *n*-pentane with aluminum chloride at about 100°, and (*b*) heating *n*-pentane at about 400° to 500°?

6. Define and illustrate: exothermic reaction, endothermic reaction, heat of combustion, kilogram calorie.

7. What conditions would you use in order to chlorinate *n*-pentane? What products would you expect to obtain from the reaction?

8. If 3.6 g of a certain paraffin hydrocarbon at 100° and 760 mm occupies 153 ml, what is the molecular weight of the hydrocarbon?

9. (Optional.) From the data in the table on page 45 show that the heat of formation of 1 mole of dimethyl ether from 2 moles of methyl alcohol in

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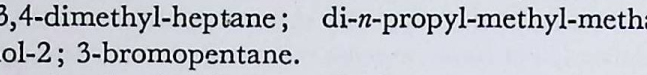
the gaseous state at 25° and 760 mm pressure is about 17.6 kg-cal, or



$$2CH_3OH(g) \longrightarrow CH_3OCH_3(g) + H_2O(l) + 17.6 \text{ kg-cal}$$

The water formed in the reaction is in the liquid state.

10. Define: hydrocarbon, Wurtz reaction, halogenation, thermal decomposition.

11. Write the structural formulas for: tetraethyl-methane; *n*-hexane; isobutane; 3,4-dimethyl-heptane; di-*n*-propyl-methyl-methane; 3,3-dimethyl-hexanol-2; 3-bromopentane.

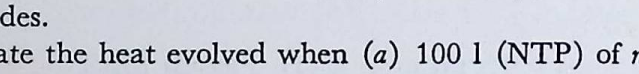
12. By what simple chemical or physical tests could you differentiate between: (*a*) pentane and eicosane (normal $C_{20}H_{42}$), (*b*) *n*-propyl ether and *n*-hexane, (*c*) *n*-amyl alcohol and *n*-octane?

13. Which of these reagents would you expect to react with *n*-pentane, *n*-amyl alcohol, *n*-butyl bromide, and *n*-butyl ether: (*a*) concentrated sulfuric acid, (*b*) dilute potassium hydroxide, (*c*) iodine, (*d*) hydrogen iodide, (*e*) metallic potassium?

14. A substance on analysis was shown to have the composition: C, 85.72; H, 14.28. What type of compound is this and what is its general formula?

15. List the common reactions of: (*a*) paraffins, (*b*) alcohols, (*c*) ethers, (*d*) alkyl halides.

16. Calculate the heat evolved when (*a*) 100 l (NTP) of *n*-pentane and (*b*) a mixture of 100 l of ethane and 100 l of propane are each completely burned. Compare the results and interpret the difference between the two values. What would be the heat evolved or absorbed if the following reaction could be made to proceed at room temperature:



$$CH_3CH_2CH_2CH_2CH_3 + H_2 \longrightarrow C_2H_8 + C_2H_6?$$

The heat of combustion of one mole of hydrogen to liquid water is 68.4 kg-cal.

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Chapter 4

UNSATURATED HYDROCARBONS

In this chapter we shall consider several classes of hydrocarbons which contain less hydrogen than the corresponding paraffin hydrocarbons. These hydrocarbons combine with bromine and chlorine and, in the presence of suitable catalysts, with hydrogen; therefore they are spoken of as *unsaturated hydrocarbons.*

OLEFINS

The simplest unsaturated hydrocarbons are the members of the olefin or ethylene series. Because the products of the action of chlorine on these unsaturated hydrocarbons were oily liquids, the hydrocarbons themselves were called *olefiant* or *oil-making* hydrocarbons. The word *olefiant* was later changed to *olefin.* The members of this series have the general formula C_nH_{2n}; the first member is **ethylene,** C_2H_4, the next **propylene,** C_3H_6. It will be noticed that they contain two less hydrogen atoms than the corresponding members of the methane series (ethane C_2H_6, propane C_3H_8).

The Structure of Ethylene. The olefins combine with bromine or chlorine in such a way that a dibromide or dichloride is formed by the addition of two atoms of the element.

$$\underset{\text{Ethylene}}{C_2H_4} + Br_2 \longrightarrow \underset{\text{Ethylene dibromide}}{C_2H_4Br_2}$$

$$C_2H_4 + Cl_2 \longrightarrow \underset{\text{Ethylene dichloride}}{C_2H_4Cl_2}$$

This is an **addition reaction.** A chemical study of the addition products has shown that they must have the structural formulas CH_2BrCH_2Br and CH_2ClCH_2Cl, respectively. The evidence for this will be presented in a later chapter (p. 148). For the present, let us assume that the formula of ethylene dibromide is correct and consider the structure of the hydrocarbon.

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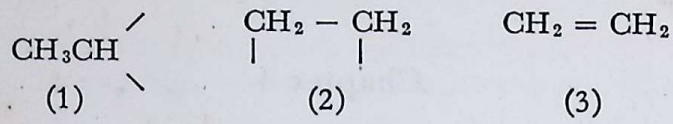
If we attempt to write a structural formula for ethylene, we are confronted by the following possibilities:



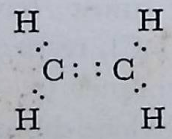
(1) (2) (3)

Formulas 1 and 2 may also be written as CH_3CH and CH_2CH_2 respectively. The "free bonds" merely express our knowledge that carbon may have a valence of four. Corresponding to formula 1 we would write PCl_3 for phosphorus trichloride since we know that phosphorus may take on five atoms as in PCl_5.

Since ethylene dibromide has the structure CH_2BrCH_2Br formula 1 is ruled out, because such a substance would add bromine to form CH_3CHBr_2. If formula 2 were correct, one would expect to find other compounds containing a trivalent carbon atom, for example, $CH_3CH_2CH_2-$ (or $CH_3CH_2CH_2$). With the exception of certain very special compounds, whose behavior is quite unlike that of ethylene and which are considered in Chap. 27, we know of no compounds containing trivalent carbon. Free methyl, CH_3, and free ethyl, C_2H_5, have never been isolated though they are capable of existing in the gaseous state for a very short time. In every ethylenic compound where one might be inclined to write a carbon atom with only three bonds, the *apparently trivalent carbon atoms occur in pairs side by side*. There is, therefore, every reason to believe that, in some way, the missing valences of the carbon atoms are bound to each other. We indicate this opinion by writing a double bond.

The double bond is a convention signifying to the organic chemist the existence of two atoms, side by side, each of which may add an additional monovalent atom or group. The double linkage is often spoken of as *a point of unsaturation*. Compounds with a double bond enter into many reactions in which they pass into compounds with single linkages.

Electronic Formula of Ethylene. The double bond, which was written by organic chemists to describe the linkage between the



Electronic formula of ethylene

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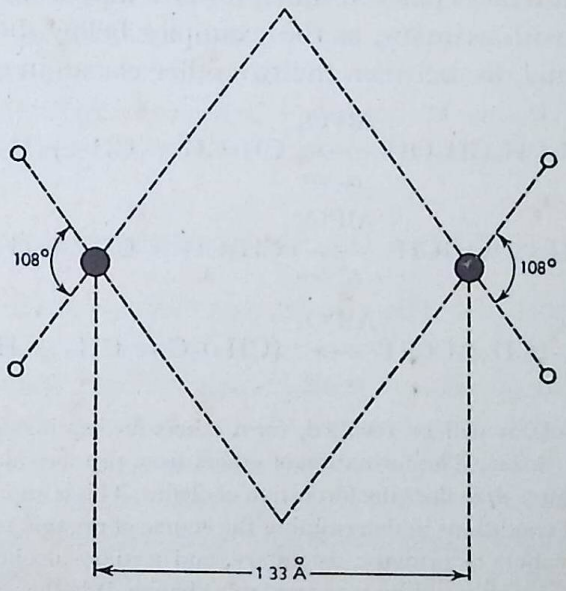
carbon atoms in ethylene long before the development of the electronic theory of valence, has been confirmed by the modern evidence of physics. It seems quite clear that there are four electrons shared in common between the carbon atoms of ethylene, therefore the idea that a single linkage represented by a bond is equivalent to one pair of electrons holds here as in the saturated compounds.

If we make a model of ethylene or a higher member of the ethylene series, adopting the convention previously used, we see that the linkage between the atoms is like the joining of two tetrahedra by a side. The study of the spatial arrangement of the atoms in compounds containing a double bond (by X-ray and electron diffraction) confirms this idea; the bond between the two doubly linked carbon atoms is shorter than the distance between two singly linked carbon atoms, namely 1.33 Å instead of 1.54 Å. This is not brought out if we use the same conventional tetrahedra for singly and doubly linked carbon atoms in constructing models. To show this shorter distance between doubly bonded carbon atoms we must use models that differentiate between doubly and singly linked carbon atoms. Such models are available and a two-dimensional picture of such a model of ethylene is shown below.



The dotted lines representing valence bonds are purely formal; actually between the two carbon centers are four electrons, which, with the four other electrons about each carbon, make an octet. Models will make it clear that the centers of all the hydrogen atoms lie in one plane, which, in the diagram above, is at right angles to the paper. Unlike the single bond, the double bond does not permit free rotation of the two atoms involved in the linkage. Certain consequences of this in terms of isomerism will be considered later.

Preparation of Olefins. The methods of preparing olefin hydrocarbons start with our common alcohols or substances easily made

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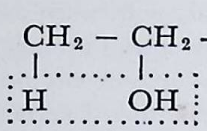
from them. All the reactions employed may be considered as elimination reactions; two atoms or groups are "split out" from the molecule leaving a double bond in their place.

Dehydration of Alcohols. In the preparation of ethylene, alcohol vapor is passed through a hot tube containing aluminum oxide or through a tower of coke impregnated with glacial phosphoric acid. These catalysts cause the dehydration of the alcohol.



$$CH_2 - CH_2 \xrightarrow[360^\circ]{Al_2O_3} CH_2 = CH_2 + H_2O$$

This is a general and excellent method of preparing a great variety of olefins. Primary, secondary, and tertiary alcohols may be employed and, depending on the nature of the alkyl groups attached to the carbinol carbon atom, different substituted ethylenes will be formed. Olefin formation takes place at much lower temperatures with tertiary alcohols than with primary, as the examples below show. Secondary alcohols, as usual, lie between the two other classes in their behavior.

$$CH_3CH_2CH_2OH \xrightarrow[\text{ca. } 300^\circ]{AlPO_4} CH_3CH = CH_2 + H_2O$$

$$CH_3CHOHCH_3 \xrightarrow[\text{ca. } 250^\circ]{AlPO_4} CH_3CH = CH_2 + H_2O$$

$$(CH_3)_3COH \xrightarrow[\text{ca. } 150^\circ]{AlPO_4} (CH_3)_2C = CH_2 + H_2O$$

Primary alcohols, it will be recalled, form ethers on heating in the presence of suitable catalysts (p. 33). The formation of ethers from primary alcohols takes place at lower temperatures than does the formation of olefins. This is another illustration of the importance of conditions in determining the course of organic reactions. Without any catalyst the vapors of primary, secondary, and tertiary alcohols can be heated to as much as 300° for hours without appreciable change. Whether, in the presence of a catalyst, ether formation or olefin formation takes place is a matter of the relative *rates* of the competing reactions. With primary alcohols at temperatures around 250°, ether formation is more rapid than olefin formation. But with secondary and tertiary alcohols, dehydration to form an unsaturated compound is already so rapid at 250° or below that this reaction predominates.

An indirect method of dehydrating alcohols is to treat them with sulfuric acid; the ester thus formed usually decomposes upon heating with the formation of an olefin and sulfuric acid. This older method,

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illustrated by the following example, is now largely superseded by the catalytic method.

$$CH_3CH_2OSO_2OH \xrightarrow{\text{Above } 150^\circ} CH_2 = CH_2 + H_2SO_4$$

The ester written above is also an intermediate in the formation of ethyl ether from ethyl alcohol (p. 30). This fact is one more illustration of the importance of experimental conditions on the course of organic reactions.

Preparation from Alkyl Halides. An alcoholic solution of potassium or sodium hydroxide acts on an ethyl halide as follows:

$$KOH + \underset{\underset{H}{|}}{CH_2} - \underset{\underset{X}{|}}{CH_2} \longrightarrow CH_2 = CH_2 + KX + H_2O$$

It will be noted that, in the production of ethylene by this method, hydrogen iodide has been eliminated from the molecule of ethyl iodide. It has been found that by the action of strong alkalies at elevated temperatures all alkyl halides which have a hydrogen atom adjacent to the halogen atom lose a molecule of halogen acid. Another example of this reaction is the formation of isobutene from tertiary butyl chloride.

$$(CH_3)_3CCl + KOH \longrightarrow (CH_3)_2C = CH_2 + KCl + H_2O$$

Just as the tertiary alcohols are catalytically dehydrated at a lower temperature than secondary or primary, so too the corresponding halides react more rapidly with alkalies with the formation of unsaturated hydrocarbons. It should be noticed that the elimination of halogen acids from alkyl halides, and the elimination of water from alcohols to form olefins, takes place between two adjacent carbon atoms, and therefore can occur only when these elements are present on adjacent carbon atoms.

Preparation from Paraffin Hydrocarbons. On heating the saturated hydrocarbons to a high temperature, particularly in the presence of a catalyst, unsaturated hydrocarbons are formed (p. 42). Hydrogen and also smaller hydrocarbon molecules such as methane and ethane are eliminated under these conditions. Since the process always yields several products it is not a useful laboratory procedure. Its significance in industry will be emphasized in Chap. 6.

Preparation from Dihalides. The addition product of an olefin and bromine gives up its bromine atoms when treated with zinc.

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This is a convenient laboratory method of preparing ethylene and is a general method for all olefins.

$$CH_2BrCH_2Br + Zn \longrightarrow CH_2 = CH_2 + ZnBr_2$$

$$R_2CBrCBrR_2 + Zn \longrightarrow R_2C = CR_2 + ZnBr_2$$

One might be tempted to imagine that in the elimination of halogen acid from alkyl halides or the elimination of bromine from the dibromide a very simple mechanism is involved. Thus it might be thought that the function of the inorganic reagent was merely to combine with free halogen acid or free bromine slowly liberated from the organic halide. This is clearly not so, however, for otherwise it would make no difference what alkali were used to combine with the acid or what metal to take up the halogen. Actually it makes a great deal of difference. For example, primary alkyl halides will not form olefins when heated with sodium carbonate (or a base of similar strength) although such a base would neutralize a halogen acid as well as sodium hydroxide. Metallic mercury combines rapidly with free bromine, but it is not effective in removing bromine from most dibromides even at an elevated temperature. The actual mechanism of all these reactions is complicated and not fully understood; very probably there are several paths which lead to the same product. In an elementary course it is very usual to write such diagrams as the following:

$$(CH_3)_2C \;\boxed{H \;\; CH_2 \;\; I} \longrightarrow (CH_3)_2C = CH_2 + HI$$

The student should be on his guard lest he confuse such a pictorial representation with the real mechanism of the reaction which is certainly much more complex.

BOILING POINTS OF THE SIMPLER ETHYLENE HYDROCARBONS

Molecular Formula	*Name*	*Structural Formula*	*Boiling Point*
C_2H_4	Ethylene	$CH_2 = CH_2$	−104°
C_3H_6	Propylene	$CH_3CH = CH_2$	− 47°
	Isomeric Butenes		
C_4H_8	Sym. dimethylethylene	$CH_3CH = CHCH_3$	+ 1°
	Unsym. dimethylethylene	$(CH_3)_2C = CH_2$	− 6.6°
	Ethylethylene	$CH_3CH_2CH = CH_2$	− 6.7°
	Isomeric Pentenes		
C_5H_{10}	Sym. methylethylethylene	$CH_3CH = CHCH_2CH_3$	+ 36°
	Unsym. methylethylethylene	$CH_3CH_2(CH_3)C = CH_2$	32°
	n-Propylethylene	$CH_3CH_2CH_2CH = CH_2$	39°
	Isopropylethylene	$(CH_3)_2CHCH = CH_2$	20°
	Trimethylethylene	$(CH_3)_2C = CHCH_3$	38°

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Physical Properties of Isomeric Olefins. The number of isomers is much greater in the olefin than in the paraffin series. This is illustrated by comparing the number of butenes and pentenes with the corresponding butanes and pentanes.

A comparison of the table on page 54 with the one on page 37 shows that the boiling points of the olefins are very close to those of the corresponding paraffins. Two hydrogen atoms make very little difference in this physical property. Like all other hydrocarbons the olefins are insoluble in water.

Nomenclature. The ethylenic hydrocarbons are named according to the Geneva system as follows: The longest unbranched carbon chain which includes the ethylenic linkage is named as in the saturated hydrocarbons, but the ending is changed from *-ane* to *-ene*. The position of substituent alkyl groups is indicated as in the saturated hydrocarbons; the position of the double bond is shown by a number following the name. This number indicates the *lower numbered of the two carbon atoms involved in the double linkage*. The numbering is always begun at the end of the chain nearer the double bond. The following examples illustrate the method: $CH_3CH_2CH = CH_2$, butene-1; $CH_3CH = CHCH_3$, butene-2; $CH_3CH = CH\underset{\underset{CH_3}{|}}{C}HCH_3$, 4-methylpentene-2; $(CH_3)_2C = CH_2$, 2-methylpropene-1; $(CH_3)_2C = CH - \underset{\underset{CH_3}{|}}{C}HCH_2CH_3$, 2,4-dimethylhexene-2.

The simplest ethylenic hydrocarbons, ethylene and propylene, still carry names that antedate the Geneva system. Many ethylenic hydrocarbons are conveniently named as alkyl derivatives of ethylene. This method of naming is adequately illustrated in the table above.

Ethylene. The first member of the olefin series is a colorless gas with a characteristic sweetish odor. It burns with a luminous, smoky flame. With air or oxygen it forms a highly explosive mixture. It is usually present in illuminating gas to the extent of a few per cent.

Ethylene is obtained today from the gases liberated during the cracking process in gasoline production (p. 109). It is also produced from natural gas, which is a mixture of gaseous paraffins, by cracking under special conditions. The separation of ethylene from the other products is readily accomplished.

Ethylene is used by growers of citrus fruits since exposure of a

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green-colored fruit to an atmosphere of ethylene develops the highest yellow or orange color. Ethylene also finds use as an anesthetic and in some respects it is superior to ether.

Chemical Properties. The olefins combine with a variety of substances to form addition products which are derivatives of the paraffin hydrocarbons. These reactions are known as *addition reactions*, and the substances which add to the ethylenic linkage are referred to as *addends*. We shall consider next a number of the more important addition reactions of the olefins.

Hydrogenation. The double bond may be saturated with hydrogen by a process known as *catalytic hydrogenation*.

In this process the hydrocarbon, alone or in solution in an inert solvent, is shaken with hydrogen in the presence of highly active forms of platinum or palladium. These catalysts cause the hydrogen to combine with the unsaturated hydrocarbons. Less expensive but also less effective is finely divided nickel whose use generally requires both high temperatures and pressures or a vapor phase reduction. However, a highly active nickel catalyst can be made which will bring about the hydrogenation of many ethylenic hydrocarbons in the cold. With ethylene the reaction may be written as follows:

$$CH_2 = CH_2 + H_2 \xrightarrow{\text{Catalyst}} CH_3CH_3$$

The catalytic hydrogenation of olefin hydrocarbons provides a method of preparing pure members of the paraffin series.

The reaction between hydrogen and an olefin runs to essential completion at room temperature or slightly higher in the presence of a suitable catalyst. The heat evolved in such hydrogenations has been measured with considerable accuracy. This is one of the few organic reactions (apart from combustion) where such measurements can be made, for hydrogenation is relatively rapid under the proper conditions, is complete, and there are no side reactions. The values of the heat of reaction thus obtained agree quite well with those calculated from the heats of combustion of the saturated and unsaturated hydrocarbons. The energy change is large, as for example:

$$CH_2 = CH_2(g) + H_2(g) \longrightarrow CH_3CH_3(g) + 33 \text{ kg-cal at room temperature}$$

Substitution of all four hydrogen atoms by methyl groups does not change the value greatly.

$$(CH_3)_2C = C(CH_3)_2(g) + H_2(g) \longrightarrow (CH_3)_2CHCH(CH_3)_2(g) + 27 \text{ kg-cal}$$

The symbol (g) indicates that the substance so marked is in the gaseous state when the value of the heat evolved is as given.

It will be recalled that only 1.7 kg-cal of heat was evolved or absorbed in the

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isomerization of *n*-butane to isobutane and vice versa, and this reaction came to equilibrium with measurable amounts of product and reactants. The heat evolved in reactions which are nearly balanced (proceed to a measurable equilibrium) at or near *room temperature* is relatively small; while reactions with large heat evolution (greater than 20 kg-cal) go to completion at room temperature *once started*. This last reservation is of the utmost importance. There is no general relation between the speed of a reaction and the amount of energy released. Nor can one predict the conditions necessary to bring about a reaction at appreciable speed (e.g., the solvent or catalyst) from a knowledge of the heat evolved. In spite of this we shall see that a knowledge of the heat of reaction is often of great practical importance.

Addition of Halogens and Hypohalogen Acids. Chlorine and bromine combine with the members of the olefin series.

$$CH_2 = CH_2 + Br_2 \longrightarrow CH_2BrCH_2Br$$

With iodine the reaction is very slow except in the presence of strong light. Under suitable conditions of illumination an equilibrium is reached which may be approached from both sides.

$$CH_2 = CH_2 + I_2 \overset{\text{Light}}{\rightleftharpoons} CH_2ICH_2I$$

At temperatures of 100° to 150° (in the gas phase) the reaction between ethylene and iodine is rapid, but the equilibrium is very unfavorable to the formation of the di-iodide. The reaction between halogens and unsaturated hydrocarbons may be carried out in some inert solvents, such as carbon tetrachloride (CCl_4) or carbon disulfide (CS_2) or in water.

In the latter solvent, another reaction also takes place at the same time. An aqueous solution of bromine or chlorine always contains some hypobromous or hypochlorous acids.

$$Br_2 + H_2O \rightleftharpoons HOBr + HBr$$

These hypohalogen acids also add to the double linkage. Thus, if ethylene is passed into bromine water, both reactions written below take place.

$$CH_2 = CH_2 + Br_2 \longrightarrow CH_2BrCH_2Br$$
$$CH_2 = CH_2 + HOBr \longrightarrow CH_2OHCH_2Br$$

By controlling the concentration of the halogen and the acidity, it is possible to make the latter reaction predominate. The preparation of CH_2ClCH_2OH, ethylene chlorohydrin, is now carried out commercially (p. 199).

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When simple ethylenic hydrocarbons react with chlorine at temperatures above 250° and in the presence of small amounts of oxygen, substitution rather than addition takes place. Propylene, for example, furnishes predominantly allyl chloride.

$$CH_2 = CHCH_3 + Cl_2 \xrightarrow[\text{Small amount of oxygen}]{250°\text{–}300°} CH_2 = CHCH_2Cl + HCl$$

Oxygen is a catalyst for the substitution reaction and it inhibits the addition of chlorine. The rate of the substitution reaction increases more with a given temperature rise than does the rate of the addition reaction. Consequently, by a suitable choice of temperature and catalyst the reaction between chlorine and simple ethylenic hydrocarbons may be directed to furnish either addition or substitution products.

Addition of Acids. Ethylene is absorbed by warm concentrated sulfuric acid. The other members of the series react even at room temperature. The product is an alkyl sulfuric acid which we have already met a number of times (pp. 30, 53).

$$CH_2 = CH_2 + H_2SO_4 \longrightarrow CH_3CH_2OSO_3H$$

If propylene is employed, the chief product is the *isopropyl* ester of sulfuric acid.

$$CH_3CH = CH_2 + H_2SO_4 \longrightarrow CH_3CH(OSO_3H)CH_3$$

The halogen acids also add to olefin hydrocarbons, forming alkyl halides. The reaction proceeds most rapidly with the higher members of the olefin series and more rapidly with hydrogen iodide or bromide than with hydrogen chloride.

$$CH_3CH = CH_2 + HI \longrightarrow CH_3CHICH_3$$

The addition of unsymmetrical reagents, like the halogen acids, to unsymmetrical derivatives of ethylene raises a problem concerning the *mode* of addition. Thus, in the examples given above, isopropyl alcohol and isopropyl bromide, not propyl alcohol and propyl bromide, are formed. The generalization which describes the mode of addition of unsymmetrical reagents to unsaturated hydrocarbons is known as *Markownikoff's rule*. It may be stated as follows: *In the addition of a compound of the type HA(A = Cl, Br, I, OSO_3H, etc.) to an ethylenic hydrocarbon, H adds to the ethylenic carbon atom which already holds the*

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greater number of hydrogen atoms. Careful experiment has shown that in many reactions a small amount of the isomer, formed by the other mode of addition, is also produced, the ratio of the two isomers depending to some extent on the nature of the solvent. It should be carefully noted that *this rule applies only to hydrocarbons;* we shall see in a later chapter that another principle is involved in the addition reactions of certain unsaturated acids, esters, and ketones.

When we consider the mode of addition of the hypohalogen acids to unsymmetrical derivatives of ethylene, we find that the halogen atom joins the carbon holding the greater number of hydrogen atoms.

$$CH_3CH = CH_2 + HOCl \longrightarrow CH_3CHOHCH_2Cl$$

Here again the rule predicts only the major product; some of the isomer is often formed. A common explanation of the fact that the halogen atom in the halogen acids and hypohalogen acids behave differently is to consider that in the one the halogen is negatively charged as compared to the hydrogen (H^+Br^-); in the other it is positively charged with respect to the OH group (HO^-Br^+). One can then say that the *positive* atom or group attaches itself to the least substituted carbon atom. Although hydrobromic acid dissociates into ions which carry the appropriate charges required by this explanation, there is no evidence that hypobromous acid dissociates to form a positive bromine ion; it actually forms the ions H^+ and OBr^-. Nevertheless, within the undissociated molecule there tends to be a distribution of electrons which corresponds to the symbol HO^-Br^+.

It has been found that the mode of addition of hydrobromic acid to simple olefin hydrocarbons containing a terminal carbon-carbon double bond may be reversed by the addition of organic peroxides (p. 501). During ordinary manipulations, or better still in the presence of antioxidants (p. 484), isobutylene and hydrogen bromide give tertiary butyl bromide in accordance with Markownikoff's rule. If, however, organic peroxides are present, isobutyl bromide predominates in the product. The following reactions summarize these facts.

$$\underset{\text{Tertiary butyl bromide}}{(CH_3)_3CBr} \xleftarrow[\text{Absence of peroxide}]{HBr} \underset{\text{Isobutylene}}{(CH_3)_2C = CH_2} \xrightarrow[\text{Presence of peroxides}]{HBr} \underset{\text{Isobutyl bromide}}{(CH_3)_2CHCH_2Br}$$

The difference in mode of addition of hydrogen bromide in the presence and absence of a peroxide indicates a different mechanism of reaction. It seems probable that the addition of the halogen acids, the hypohalogen acids (HOX), and the halogens starts by the more positive end of the reacting molecule joining the ethylenic carbon atom having the more hydrogen atoms; the negative ion then adds to the other carbon atom. Whether dissociation into ions takes place before or after the molecules react or at the same moment would be difficult to decide; we do know that all the substances involved are to some degree polar molecules and can be thought of as having a somewhat ionic bond under all conditions, with the polarities as indicated:

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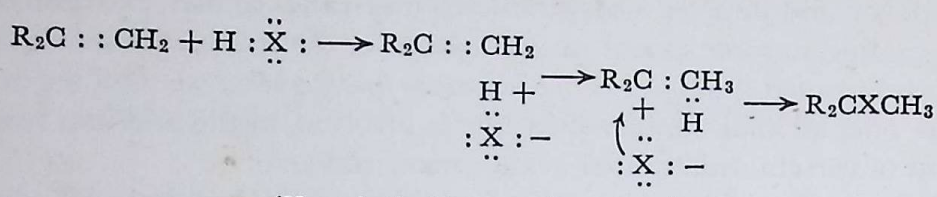
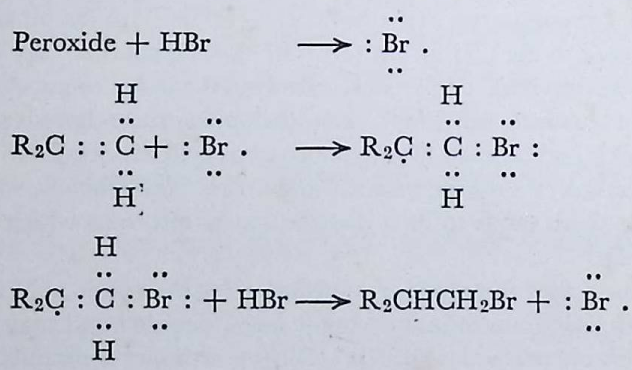
$\overset{+}{H}\overset{-}{X}$, $\overset{+}{B}r\overset{-}{O}H$, $\overset{+}{B}r\overset{-}{B}r$. On this basis the following mechanism for the normal addition has been suggested.



(Hypothetical intermediate steps.)

According to these same ideas, free bromine atoms or their equivalent are formed by the interaction of the peroxide and hydrobromic acid. The free bromine atom is electrically neutral but carries an unshared electron. Interaction of such an atom (whose existence would be very fleeting) with an olefin produces a substance of transitory existence containing one bromine atom attached to carbon and also an unshared electron. This in turn liberates a bromine atom from a molecule of hydrogen bromide and so the reaction goes on in a sort of *chain*.



It is assumed that in both the normal and the abnormal reaction the first point of addition is the carbon atom holding the greater number of hydrogen atoms, but in the two reactions a *different* atom first adds. Chain reactions of this type will be met with again.

Oxidation. Olefins are oxidized by potassium permanganate ($KMnO_4$) to compounds containing two hydroxyl groups. The hydrocarbon is shaken with the permanganate solution. The equation[1] for the reaction with ethylene is:

$$CH_2 = CH_2 + [O] + H_2O \xrightarrow{KMnO_4} \underset{\text{Ethylene glycol}}{CH_2OHCH_2OH}$$

The product is **ethylene glycol;** it is further oxidized to carbon dioxide and water unless the solution is cold and dilute. The final products

[1] The symbol [O] will be used throughout this book to indicate oxygen from an oxidizing agent; the oxidizing agent is written over the arrow.

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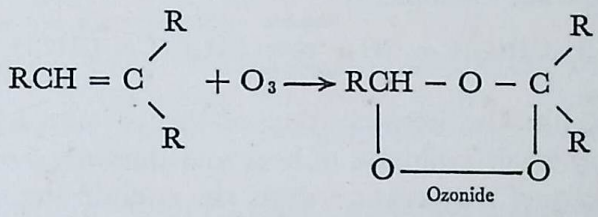
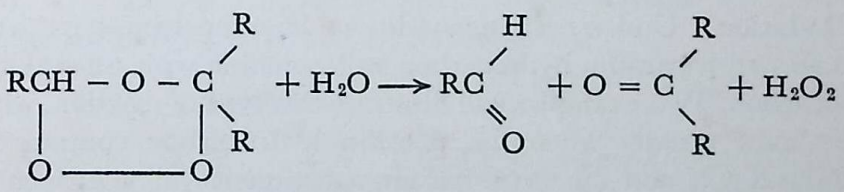
of oxidation of an olefin depend upon the number and position of the substituents: the group $CH_2 =$ is oxidized to carbon dioxide and water, the group $RCH =$ to an organic acid of the formula RCOOH, and the group $\begin{matrix} R \diagdown \\ R \diagup \end{matrix} C =$ to a ketone of the formula $\begin{matrix} R \diagdown \\ R \diagup \end{matrix} C = O$. This makes it possible to determine the structure of an olefin by oxidizing and identifying the oxidation products. For example, $CH_3CH_2CH = CH_2$ on oxidation furnishes CH_3CH_2COOH, CO_2, and H_2O; while the isomeric $CH_3CH = CHCH_3$ furnishes two molecules of CH_3COOH.

The reaction with ozone, O_3, is an even more valuable method for oxidizing an olefin in such a way as to establish its structure. An olefin reacts with ozone to furnish an ozonide.



An ozonide will react with water to form hydrogen peroxide and, depending on the number and position of the substituents present in the olefin, aldehydes, $RC\begin{matrix} H \\ O \end{matrix}$, or ketones, $\begin{matrix} R \diagdown \\ R \diagup \end{matrix} C = O$.



By identifying the aldehydes or ketones formed, the structure of the olefin is established, for the over-all process is

$$\rangle C = C \langle \longrightarrow \rangle C = O + O = C \langle$$

and from the fragments it is easy to deduce the structure of the olefin.

In practice the oxidation of an olefin with ozone, which is known as *ozonization*, is done by passing a stream of oxygen containing from 6 to 10 per cent of ozone through a solution of the olefin in a solvent, such as ethyl bromide, which is not attacked by ozone. Since ozonides are unstable and explosive they are not isolated. Since hydrogen

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peroxide reacts with some aldehydes and ketones, the ozonides are not decomposed with water alone, but with water and a reducing agent which will react with the hydrogen peroxide. Sodium bisulfite solution or a suspension of zinc dust in water can be used for this purpose.

Ethylene itself will add oxygen at high temperatures in the presence of a silver catalyst. The reaction is the basis for a number of important industrial syntheses.

$$CH_2 = CH_2 + \tfrac{1}{2}O_2 \xrightarrow[250^\circ]{Ag} \underset{O}{CH_2 - CH_2}$$

Isomerization. In the presence of catalysts and at elevated temperatures, ethylenic hydrocarbons may isomerize by a shift of the double linkage. For example,

$$CH_3CH_2CH = CH_2 \underset{600^\circ\text{–}700^\circ}{\overset{\text{Catalyst}}{\rightleftharpoons}} CH_3CH = CHCH_3$$

The reaction, like the isomerization of the paraffin hydrocarbons, involves a very small evolution of heat and does not run to completion; an increase of temperature shifts the equilibrium somewhat to the left. The shift of the double bond may be combined with the change in the carbon chain structure characteristic of the isomerization of the saturated compounds. When this occurs a complicated set of products are in equilibrium with each other in the presence of catalysts at temperatures of 400° to 700°.

Alkylation. Under certain conditions of temperature, pressure, and catalyst, a paraffin hydrocarbon will combine with an ethylenic hydrocarbon. Two examples will illustrate this type of reaction, which occurs most rapidly when the paraffin hydrocarbon contains the grouping R_3CH and the olefin has few substituents (alkyl groups) on the ethylenic carbon atoms.

1. (*a*) $$CH_3\overset{H}{C}HCH_3 + CH_2 = CH_2 \xrightarrow[500^\circ;\ 300\ \text{atm}]{\text{No catalyst}} \underset{\text{Isopentane}}{CH_3CH_2CH(CH_3)_2}$$

(*b*) $$CH_3CH_2\overset{H}{C}H_2 + CH_2 = CH_2 \xrightarrow[500^\circ;\ 300\ \text{atm}]{\text{No catalyst}} CH_3CH_2CH_2CH_2CH_3$$

This first example shows that a normal saturated hydrocarbon can behave in two ways: either the hydrogen atom of a terminal CH_3 group or the hydrogen atom of a CH_2 group may react.

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$$2.\ (CH_3)_3CH + CH_3CH{=}CHCH_3 \xrightarrow[\text{Also concd. } H_2SO_4 \text{ at } 25^\circ\text{, operating under pressure}]{AlCl_3 \text{ at } 30^\circ} \begin{cases} (CH_3)_3CCH_2CH(CH_3)_2 \\ (CH_3)_2CHCHCH(CH_3)_2 \\ \qquad\qquad | \\ \qquad\qquad CH_3 \\ (CH_3)_2CHC(CH_3)CH_2CH_3 \\ \qquad\qquad | \\ \qquad\qquad CH_3 \\ CH_3CHCH_2CH_2CH_3 \\ \quad | \\ (CH_3)_3C \end{cases}$$

This second example shows that isomerization (p. 41) may accompany alkylation. The reaction is even more complex than the equation indicates, for paraffins containing from five to more than nine carbon atoms are also formed.

Finally it should be noted that alkylation is an addition reaction, the reverse of the decomposition reactions referred to as *cracking* (p. 42). Whether thermal (example 1) or catalytic (example 2), alkylation takes place at much lower temperatures than the reverse reaction of decomposition.

Polymerization. When ethylene as a liquid under very high pressure (1000 atm) is heated to 100° to 400° with small amounts of oxygen, many molecules combine in a long chain. The product has an average molecular weight of 2000 to 20,000 depending on the temperature and pressure. Products of such high molecular weight formed from simple compounds are known as *polymers*. The reaction is called *polymerization*. It may be formulated as:

$$nCH_2 = CH_2 \xrightarrow[\substack{1000 \text{ atm} \\ 100^\circ\text{–}400^\circ}]{\substack{\text{Small amount} \\ \text{of } O_2}} (CH_2CH_2)_n, \text{ where } n = 70 \text{ to } 700$$

The product is of importance commercially and is known as *Polythene*. It is a tough solid melting around 118°, and has very valuable properties as an insulator which made it of great importance in radar during World War II.

It seems quite clear that in the polymerization a great number of ethylene molecules have joined together in a chain. This type of polymerization is known as *addition polymerization*. It is not certain what is at the ends of the chain, and the molecule is so large that we have difficulty in finding out by ordinary chemical methods. This is a frequent dilemma in the study of polymerization reactions. If we

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wish to write a formula for the polymerized ethylene we can leave this question unanswered.

$$? - CH_2CH_2(CH_2CH_2)_xCH_2CH_2 - ?$$

Or, we may assume some sort of shift of hydrogen atoms.

$$CH_3CH_2(CH_2CH_2)_xCH = CH_2$$

To detect one double bond among 70 to 700 single bonds per molecule would be difficult, but the double bond may not be present in the final molecule since reaction with the little oxygen present may convert it to some saturated compound.

Products similar to polythene have not been produced as yet from the higher olefins. But under a different set of conditions (with aluminum chloride as a catalyst and at temperatures below $-35°$), isobutylene polymerizes to an important product, polyisobutylene, which we shall consider when we discuss synthetic rubber.

$$2n(CH_3)_2C = CH_2 \xrightarrow[-35 \text{ to } -100°]{AlCl_3} \left[-\overset{\displaystyle CH_3}{\underset{\displaystyle CH_3}{\overset{|}{\underset{|}{C}}}}CH_2\overset{\displaystyle CH_3}{\underset{\displaystyle CH_3}{\overset{|}{\underset{|}{C}}}}CH_2- \right]_n \quad n = 500\text{–}800$$

POLYISOBUTYLENE

Molecular weight 25,000 to 40,000

The product is a thick liquid or a tough elastic solid depending on its molecular weight.

Polymeric substances (i.e., polymers) are frequently obtained when the olefins are heated with powerful catalysts such as aluminum chloride or concentrated sulfuric acid. Such products are often formed as undesirable byproducts in other reactions of hydrocarbons. Unless the conditions of polymerization are carefully controlled the product consists of such a variety of polymers with different molecular weights that its properties are undesirable. Sticky, gummy, amorphous "tars" are only too readily formed in the laboratory as the chemist knows from sad experience if too powerful reagents are allowed to react too long with most organic substances. These byproducts, which can neither be crystallized nor distilled and have no useful physical properties, are the result of a series of polymerization reactions many of which involve unsaturated compounds.

Other types of polymerization reactions will be encountered later (Chaps. 11, 26).

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ACETYLENIC HYDROCARBONS

This class of hydrocarbons has the general formula C_nH_{2n-2}. The first member of this series, acetylene C_2H_2, is by far the most important.

Structure of Acetylene. Acetylene reacts with bromine and chlorine forming a compound $C_2H_2X_4$; the bromide has the structure $CHBr_2CHBr_2$.

The possible formulas for acetylene, C_2H_2, are:

$$\underset{(1)}{CH_2 = C\langle} \qquad \underset{(2)}{\begin{matrix} CH - CH \\ \langle\rangle \quad \langle\rangle \end{matrix}} \qquad \underset{(3)}{CH \equiv CH}$$

The first two, of course, may be written also as $CH_2 = C$ and $CH - CH$. The structure of the tetrabromide shows that we must write formula 2 or 3. The reasons for preferring 3 are similar to those given in favor of the double-bonded formula for ethylene (p. 50). Compounds of the type $CH_3CH_2CH\langle$ are unknown; with the exception of carbon monoxide and a few other peculiar substances, no compounds containing divalent carbon have been prepared. We therefore use a triple bond to signify the existence of two apparently divalent carbon atoms side by side. We believe that the valences are in some way joined with one another. Such compounds have the ability to add *four* monatomic atoms or groups, as the following reaction indicates.

$$CH \equiv CH + 2Br_2 \longrightarrow CHBr_2CHBr_2$$

The *electronic formula* for acetylene is H : C : : : C : H. In three dimensions this corresponds to the union of two tetrahedra by a common face. The distance between the centers of two triply linked carbon atoms is only 1.20 Å. (Compare 1.33 Å for C = C, and 1.54 Å for C — C.)

Preparation of Acetylenic Hydrocarbons. Acetylene is easily prepared from calcium carbide, CaC_2, and water.

$$CaC_2 + 2H_2O \longrightarrow CH \equiv CH + Ca(OH)_2$$

Since calcium carbide is readily made in the electric furnace from coke and lime, acetylene is one of the cheap organic chemicals available to the industrial chemist.

Acetylene and its homologs may be prepared by eliminating two

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molecules of halogen acid from a dihalide by means of molten alkali or strong solutions of potassium hydroxide. The dihalide in turn can be made from the corresponding olefin and halogen.

$$CH_3CH = CH_2 + Br_2 \longrightarrow CH_3CHBrCH_2Br$$

$$\underset{\text{Propylene dibromide}}{CH_3CHBrCH_2Br} + 2KOH \xrightarrow{\text{Heat}} \underset{\text{Methyl acetylene}}{CH_3C \equiv CH} + 2KBr + 2H_2O$$

Acetylene. Acetylene is a colorless gas, insoluble in water, with a characteristic odor. It can be condensed to a liquid which boils at $-84°$ and which is explosive if subjected to a sudden shock. For its transport it is necessary to dissolve the gas under pressure in acetone. In this form it is safe. It burns with a luminous flame when a specially constructed burner is used which allows free access of air.

Acetylene has had a varied industrial history. It was first used at the end of the last century as a lighting gas in competition with coal gas. Acetylene lamps were at one time used as bicycle and automobile lights.

The present industrial use of acetylene is as a cheap raw material from which to prepare other compounds (Chap. 8). The preparation of an artificial rubber from acetylene is discussed in Chap. 6.

Addition Reactions of Acetylene. The triple linkage in acetylene will add four monovalent atoms or groups, much as the double linkage in ethylene adds two such atoms or groups. In a few reactions, only two atoms or groups can be added and a derivative of ethylene is formed. Thus, if acetylene is passed into a water solution of chromous chloride, $CrCl_2$ (a powerful reducing agent), ethylene is formed. Certain other reducing agents enable one to prepare ethylene derivatives from acetylenic hydrocarbons. However, since ethylene and its derivatives are also reactive, usually the addition reactions do not stop at the ethylene stage. The catalytic hydrogenation of acetylene produces ethane if sufficient hydrogen is employed.

$$CH \equiv CH + H_2 \xrightarrow{\text{Catalyst}} CH_2 = CH_2 + H_2 \xrightarrow{\text{Catalyst}} CH_3CH_3$$

With chlorine, tetrachlorethane $CHCl_2CHCl_2$ is the final product.

$$CH \equiv CH + 2Cl_2 \longrightarrow CHCl_2CHCl_2$$

The halogen acids add to acetylene forming a halogen derivative of ethylene which can then combine further with another molecule; the

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final product has two halogen atoms on the same carbon atom.

$$CH \equiv CH + HCl \longrightarrow CH_2 = CHCl$$
$$CH_2 = CHCl + HCl \longrightarrow CH_3CHCl_2$$

The addition of acids to homologs of acetylene, like the addition of these same reagents to unsymmetrical olefins, follows Markownikoff's rule (p. 58).

Acetylene also adds a variety of substances (water, alcohols, phenols, acids, amines, and so on) which contain a hydrogen atom attached to some element other than carbon. Most of the addends belong to classes of compounds which we have not yet considered. We shall therefore take up only two examples of these addition reactions here, but we shall encounter other illustrations later. Most of the addition products contain the vinyl group, $CH_2 = CH-$, and the addition reactions are often referred to as *vinylation*. Many of the addition products are of industrial importance.

In the presence of mercuric ion and dilute sulfuric acid, acetylene adds a molecule of water to furnish a valuable product, acetaldehyde.

$$CH \equiv CH + H_2O \xrightarrow[H_2SO_4]{Hg^{++}} [CH_2 = CHOH] \longrightarrow \underset{\text{Acetaldehyde}}{CH_3CHO}$$

The product is considered in Chap. 7, its commercial utilization in Chap. 8. In the presence of sodium hydroxide or a sodium alkoxide, acetylene will add a molecule of alcohol to furnish an alkyl vinyl ether.

$$CH \equiv CH + CH_3OH \xrightarrow[\text{Heat-pressure}]{NaOH \text{ or } NaOCH_3} \underset{\text{Methyl vinyl ether}}{CH_2 = CHOCH_3}$$

The alkyl vinyl ethers, like so many other compounds containing the vinyl group, can be polymerized to useful products.

Acetylides. Acetylene and the members of the acetylene series which *contain the grouping* $-C \equiv CH$, enter into two characteristic reactions. When shaken with ammoniacal cuprous or silver solutions, they form precipitates of **metallic acetylides.** These are usually highly explosive in the dry state. The acetylides are related to acetylene as salts are to acids. The metal has replaced a hydrogen atom. The following equations illustrate these reactions.

$$CH \equiv CH + \underset{\text{As complex ion}}{Cu_2Cl_2} + 2NH_4OH \longrightarrow \underset{\substack{\text{Ppt.}\\ \text{copper acetylide}}}{CuC \equiv CCu} + 2NH_4Cl + 2H_2O$$

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On treatment with dilute acids, the acetylides regenerate acetylene.

$$AgC \equiv CAg + 2HNO_3 \longrightarrow CH \equiv CH + 2AgNO_3$$

Copper acetylide used as a catalyst makes possible the addition of acetylene as $H - C \equiv CH$ to carbonyl compounds (Chap. 7).

Sodium acetylide, $CH \equiv CNa$, is formed by the action of acetylene on a solution of sodium in liquid ammonia or by passing the gas through molten sodium at 180°. Disodium acetylide, C_2Na_2, can also be formed in this way. The sodium acetylides are colorless solids which are decomposed by water with the formation of acetylene.

The sodium acetylides offer another method of preparing homologs of acetylene. They react with alkyl halides in the following manner using liquid ammonia as the solvent.

$$CH_3C \equiv CH + Na \longrightarrow CH_3C \equiv CNa$$

$$CH_3C \equiv CNa + CH_3I \longrightarrow \underset{\text{Dimethyl acetylene}}{CH_3C \equiv CCH_3}$$

Acetylene liberates methane from methylmagnesium iodide when it is passed into an ethereal solution of this reagent. This is our first example of an active hydrogen atom attached directly to carbon.

$$CH \equiv CH + 2CH_3MgI \longrightarrow IMgC \equiv CMgI + 2CH_4$$

Nomenclature. According to the Geneva system acetylenic hydrocarbons are named by changing the ending *-ane* of the saturated hydrocarbon to *-ine* or *-yne;* the position of the unsaturation is indicated as in the olefins by a numeral after the name. They are also named as alkyl derivatives of acetylene. Thus $CH_3C \equiv CH$ is **propine** (also written propyne) or **methylacetylene;** it is a gas boiling at −23°. $CH_3C \equiv CCH_3$ is **dimethylacetylene** or **butine-2;** it boils at 28°. $CH_3CH_2C \equiv CH$ is **ethylacetylene** or **butine-1** (bp 14°).

DIOLEFINS

A class of hydrocarbons isomeric with the acetylenic series is the diolefin series, C_nH_{2n-2}. The members of this series contain two double linkages; the simplest member is **allene,** $CH_2 = C = CH_2$, a gas boiling at −32°.

The Butadienes. Among the most interesting and useful members of the diolefin series are the derivatives of butadiene-1,3, $CH_2 = CH - CH = CH_2$. All these compounds contain two double

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linkages connected by a single bond. *Such a system of alternate single and double linkages* is known as a *conjugated system of double bonds.* Compounds containing conjugated systems undergo a number of special reactions; one of these, the polymerization reaction, will be discussed later in connection with rubber.

The nomenclature of the diolefins is in accord with the Geneva system. The longest straight chain is named, the ending *-diene* replacing the *-ane* of the saturated hydrocarbon. The position of the two double linkages is indicated by two numerals. Thus $CH_2 = CH - CH = CH_2$ is butadiene-1,3; while $CH_2 = C = CHCH_3$ is butadiene-1,2.

Butadiene-1,3 is a gas which condenses at $-4°$. **2-Methylbutadiene-1,3 (isoprene)** boils at 34° and **2,3-dimethylbutadiene-1,3** boils at 70°.

Structure of the Diolefins. Like the acetylenes, the diolefins combine with four monovalent atoms or groups forming derivatives of the paraffin hydrocarbons. Unlike the acetylene series, however, the groups which have been added are distributed on *four different* carbon atoms. For this reason we write a structure with *two double* bonds.

$$CH_2 = CH - CH = CH_2 + 2Br_2 \longrightarrow CH_2BrCHBrCHBrCH_2Br$$

The diolefins take up two molecules of gaseous hydrogen when subjected to catalytic hydrogenation and are thus converted into the paraffin hydrocarbons. This reaction enables us to prove the way in which the carbon chain is arranged in any diolefin of unknown structure. For example, isoprene on hydrogenation yields isopentane.

$$\underset{\text{Isoprene}}{CH_2 = \underset{\underset{CH_3}{|}}{C} - CH = CH_2} + 2H_2 \xrightarrow{\text{Catalyst}} \underset{\text{Isopentane}}{CH_3\underset{\underset{CH_3}{|}}{C}HCH_2CH_3}$$

Special Reactions of Conjugated Dienes. The reactions of conjugated dienes are of extreme interest since they demonstrate the effect of two pairs of double bonds on each other when they are conjugated. Thus, when some of the homologs of butadiene are allowed to react catalytically with hydrogen, and the reaction is stopped after one mole of hydrogen is absorbed, the product obtained indicates a special type of addition.

$$(CH_3)_2C{=}CH{-}CH{=}C(CH_3)_2 + H_2 \xrightarrow{\text{Catalyst}} (CH_3)_2CH{-}CH{=}CH{-}CH(CH_3)_2$$

In this reaction one hydrogen atom has added to each carbon at the end of the conjugated system, and a double bond has formed between

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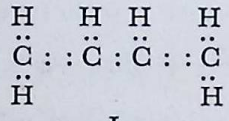
the center carbon atoms. This type of addition is known as 1,4-*addition to conjugated systems*. In many addition reactions of such diolefins a mixture of products formed by 1,4-addition to the conjugated system and 1,2-addition to one of the double bonds is obtained. The reaction of butadiene-1,3 with bromine is an example of this.

$$CH_2 = CHCH = CH_2 + Br_2 \begin{cases} \underset{\text{1,4-addition}}{CH_2BrCH = CHCH_2Br} \\ \underset{\text{1,2-addition}}{CH_2BrCHBrCH = CH_2} \end{cases}$$

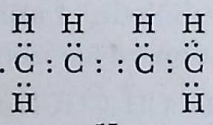
In other reactions only 1,2-addition may take place. We shall have occasion to refer to this type of addition quite frequently (p. 320). It should be emphasized that 1,4-addition may occur with compounds which have conjugated double bonds, but not with dienes which do not contain the system of alternate single and double linkages.

Following our usual convention of letting a single link represent a pair of shared electrons and a double link two pairs of shared electrons, the electronic formula for butadiene is that shown by formula I.



I

Another possibility which suggests itself in view of the 1,4 type of addition just mentioned is shown in formula II.



or $CH_2CH = CHCH_2$

II

Such a structure would correspond to the formula of the products formed when hydrogen or bromine adds to the ends of the conjugated system. But the difference between formulas I and II rests only in the position of electrons, the arrangement of all the atomic nuclei is identical. Therefore if two different substances corresponding to these two formulas existed they would represent a special type of isomer. For some years certain chemists thought that this type of isomer, called by them *electromers*, did exist. We now believe this is impossible and we believe that butadiene is not a mixture of two closely related isomers such as I and II, but is instead *one substance whose arrangement of atomic nuclei is as in both I and II and whose arrangement of electrons cannot be accurately described by either formula*. Rather the electronic structure of butadiene is a sort of hybrid between the structures represented by I and II. This phenomenon is known as *resonance* and will be considered at length in the next chapter in connection with the structure of acids. A study of the dienes shows that the arrangement of electrons given in I predominates in the true arrangement (the hybrid), so we are not far wrong in writing the conventional formula for butadiene as the equivalent of I.

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Finally, we must remark that in writing a single electron on the terminal atoms of formula II we assume that these electrons are in the same state as though they were paired; for this reason some writers refer to the existence of a "formal bond" between atoms 1 and 4 and write a dotted line connecting them.

$$\underset{\vdots\cdots\cdots\cdots\cdots\cdots\vdots}{CH_2CH = CHCH_2}$$

PHYSICAL PROPERTIES OF HYDROCARBONS AND DERIVATIVES

The forces which hold molecules together in a liquid or solid are *intermolecular forces*. The smaller these forces are, the lower are the melting and boiling points. As an extreme example one may mention helium which boils at −268.9°, very near the absolute zero; hydrogen molecules attract each other almost as little as do helium atoms and liquid hydrogen boils at −252° (both at one atmosphere pressure). Compared to these elements, the intermolecular forces involved in the most symmetrical and simplest organic compounds are large, for methane boils at −161°. Substitution of a hydrogen atom in methane by a chlorine atom or a methoxyl group ($-OCH_3$) changes the situation radically; the substitution products, methyl chloride and methyl ether, respectively, boil only a little below 0°. Introduction of an hydroxyl group, however, has the greatest effect and raises the boiling point to 65°.

A similar set of circumstances is found throughout the homologous series of paraffin hydrocarbons and their derivatives. We have already noted that, with increase in the complexity of the molecule and corresponding increase in molecular weight, the boiling points of the hydrocarbons and their derivatives rose regularly. (The melting points also rise, but are much more subject to slight changes in structure. Compare the melting and boiling points of *n*-octane and 2,2,3,3-tetramethylbutane given on page 39.) This increase in boiling point must reflect an increase in the cohesive forces between the molecules.

These forces are sometimes spoken of as *van der Waals'* forces as they correspond to one of the corrections introduced by van der Waals into the law relating volume and pressure of gases to correct for the fact that there are no perfect gases. The larger the intermolecular forces the more the vapors of the compound in question deviate from the simple gas law, PV/T = a constant.

Dipole Moments. In addition to the general intermolecular forces which attract one molecule to another and to which we have referred, other more specific interactions between molecules can often be

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identified. One of the most important of these is an electrostatic force which occurs even in many electrically neutral molecules; it is in a sense a reflection of the strong electrostatic forces which bind the ions together in polar molecules. If one end of a molecule is electrically charged with respect to the other, then the whole molecule can be considered a dipole, + —— −, and the moment of this dipole, which is the measure of its tendency to orient in an electrical field, is a product of the charge and the distance between the positive and negative centers. At first sight it would appear that all compounds with a covalent bond should have zero moments and, indeed, the dipole moments of the hydrocarbons are small. With the introduction of a halogen atom or an hydroxyl group in place of hydrogen, however, some deviations from a uniform sharing of the two electrons between the two atoms occur, and the alkyl halides and alcohols have measurable dipole moments. This can be formulated by saying that to a certain degree the carbon-halogen bond partakes of the nature of a polar bond. The link between hydrogen and oxygen in water is definitely of this nature so we find that alcohols have a dipole moment comparable to that of water. The interaction between the dipole moments of molecules adds another cohesive force. Therefore we find compounds with appreciable dipole moments, such as the alkyl halides, ethers, and water, have higher boiling points than hydrocarbons of comparable molecular weight. Thus, the effect already noted of introducing halogen atoms, ether groups, and hydroxyl groups, finds an explanation in terms of the electronic theory of valence.

The *dielectric constant* of a substance is a physical constant which can be measured for a solid, liquid, or gas. It measures the effect of a substance on the force with which two oppositely charged plates attract each other when separated by the material in question. The dielectric constant of a vacuum is taken as unity. Even those nonpolar compounds in which the electrical charges are uniformly distributed possess the property of becoming polarized in an electrical field, hence their dielectric constant is not unity but depends on the number and kind of atoms present. The dipole moment of a substance, however, has an additional effect and the greater the moment the higher the dielectric constant. The very high dielectric constants of some materials is due almost entirely to the fact that their molecules have dipole moments. Furthermore, the magnitude of this contribution to the dielectric constant depends on the temperature. By measuring the dielectric constant at several temperatures the magnitude of the dipole moment can be determined. The reason for this is that the higher the temperature in a liquid the more the thermal agitation of the molecule resists the force of the electric field tending to align the dipoles across the field.

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Certain organic compounds have surprisingly high dipole moments. For example, nitromethane has a dipole moment of 3.5×10^{-18} electrostatic units, while methyl chloride and ethyl alcohol have moments of 1.86×10^{-18} and 1.70×10^{-18} electrostatic units, respectively. These large dipole moments correspond to structures where there is a polar structure superimposed on the nonpolar structure. Such substances have correspondingly strong intermolecular forces. An extreme case is afforded by the amino acids and proteins so important in biology (Chap. 19).

Solubility. Solubility relations are of great importance in organic chemistry. They are determined by the intermolecular forces of the solute and the solvent. In general, the simple rule that like dissolves like sums up the situation; hydrocarbons dissolve other hydrocarbons. Water, containing the strong polar group $-OH$, does not mix with the hydrocarbons or their derivatives unless they contain an OH group or certain other strongly polar groups. The longer the carbon chain the more the hydrocarbon nature of the molecule predominates; thus the alcohols containing four or more carbon atoms are no longer completely miscible with water.

QUESTIONS AND PROBLEMS

1. Name the following compounds:
$CH_3CH_2CH = C(CH_3)_2$, $CH_3CH_2CH_2C \equiv CH$, $CH_2 = C = CHCH_2CH_3$, $(CH_3CH_2)_2C = C(CH_3)_2$, $CH_2 = CH - CH = CHCH_2CH_3$.

2. Compare the thermal cracking of paraffin hydrocarbons and the alkylation of ethylenic hydrocarbons.

3. A sample of a pure liquid is known to be either pentine-1 or pentadiene-1,2. What chemical test could you use to identify the sample?

4. Write balanced equations for the reactions, if any, between butene-2 and (*a*) bromine, (*b*) hydrogen and a catalyst, (*c*) hypochlorous acid, (*d*) hydrogen bromide, (*e*) sodium hydroxide. Specify the conditiops under which each reaction is to be run.

5. How could you convert butanol-1 to (*a*) butanol-2, (*b*) 2-bromobutane, (*c*) 1-bromobutane, (*d*) 1,2-dibromobutane?

6. What is the peroxide effect in the addition to ethylenic hydrocarbons?

7. An ethylenic hydrocarbon has the molecular formula C_4H_8. On ozonization it furnishes only one product. What is the structural formula of the hydrocarbon?

8. How could you prepare (*a*) propine-1 from isopropyl alcohol, (*b*) butane from *n*-butyl alcohol, and (*c*) propine-1 from acetylene and methyl alcohol.

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9. Define and give examples of polymerization.

10. A sample of a pure gas is known to be either ethane, ethylene, acetylene, or nitrogen. What chemical tests would you use to identify the gas?

11. Write equations for the ozonization of $CH_3CH_2CH = CH_2$, $(CH_3)_2C = C(CH_3)_2$, and $CH_3CH_2CH = CHCH_3$ including the decomposition of the ozonides.

12. What products would you expect to obtain from butine-1 and (*a*) hydrogen chloride, (*b*) chlorine, (*c*) ammoniacal cuprous chloride?

13. Define (*a*) dipole moment, (*b*) 1,4-addition, (*c*) conjugated system, and (*d*) average molecular weight.

14. State Markownikoff's rule and show its application to the addition reactions of both ethylenes and acetylenes.

15. Give the structures of: (*a*) 2,3-dimethyl-butadiene-1,3, (*b*) isoprene, (*c*) ethyl-methyl-acetylene, (*d*) isopropyl-ethylene, (*e*) 2-methylbutene-2.

16. Define and illustrate: (*a*) addition reaction, (*b*) substitution reaction, (*c*) catalytic hydrogenation, (*d*) acetylides, (*e*) conjugated dienes.

17. Complete the following reactions, indicating when more than one reaction may occur and, if possible, under what conditions:
(*a*) $CH_3CHBrCH_2Br + KOH$, (*b*) $CH_3C \equiv CH + CH_3MgI$,
(*c*) $(CH_3)_2C{=}CH_2{+}HBr$, (*d*) excess $CH_3CH_2OH{+}$conc. H_2SO_4(heated),
(*e*) $CH_2 = \underset{\underset{CH_3}{|}}{C} - CH = CH_2 + Br_2$.

18. Define 1,2- and 1,4-addition. Compare the reaction of 1 mole of hydrogen (in the presence of platinum catalyst) with 1 mole of hexadiene-1,3 and with 1 mole of hexadiene-1,4.

19. Contrast the behavior of primary, secondary, and tertiary alcohols with respect to dehydration and rate of reaction with the halogen acids.

20. Suggest a roughly quantitative method for determining the percentage of methane in a mixture of methane and nitrogen; of ethylene in a mixture of ethylene and ethane; of acetylene in a mixture of acetylene, ethylene, and methane.

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Chapter 5

ORGANIC ACIDS

Formic acid, HCOOH, and **acetic acid,** CH_3COOH, are the first two members of an homologous series known as the *fatty acid series.* The name arises from the fact that two of the higher members—palmitic and stearic acids—are prepared from animal fats. All the acids of the series, except the first, may be represented by the general formula RCOOH; formic acid has a hydrogen atom instead of an alkyl group. The **carboxyl group** $-\overset{\overset{\displaystyle O}{//}}{C}-OH$ is characteristic of organic acids. We will postpone a discussion of the evidence for its structure until we have learned more about the general nature of the acids of this series.

The Formation of Salts. The hydrogen atom of the carboxyl group is acidic; dilute water solutions of organic acids color blue litmus red, evolve hydrogen when acted on by metals, and are neutralized by metallic hydroxides forming salts. In terms of the electrolytic theory of dissociation we write the following ionic equilibrium.

$$RCOOH \rightleftharpoons RCOO^- + H^+$$

Most organic acids are relatively weak, i.e., the degree of the dissociation even in dilute solution is small. For example, in a tenth normal solution of acetic acid, only a few per cent of the molecules are dissociated. However, the organic acids are strong enough to displace the very weak carbonic acid from its salts. Thus sodium salts may be made from sodium hydroxide, sodium carbonate, or sodium bicarbonate.

$$RCOOH + NaOH \longrightarrow RCOONa + H_2O$$

$$2RCOOH + Na_2CO_3 \longrightarrow 2RCOONa + H_2O + CO_2$$

$$RCOOH + NaHCO_3 \longrightarrow RCOONa + H_2O + CO_2$$

Preparation of Acids from Salts. The salts of the fatty acids are nonvolatile, crystalline solids and are usually soluble in water. The

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acids are prepared from them by treating with sulfuric acid. If the acid is sufficiently volatile to be distilled, the dry salt and concentrated sulfuric acid are employed. The higher acids which distill only at high temperatures are more readily obtained from their salts by adding the mineral acid to an aqueous solution and extracting with ether. The organic acid, but not the salt, is soluble in the ether layer. This is an excellent illustration of the use of an immiscible solvent in separating an organic substance (the acid) from an aqueous solution containing inorganic material (Na_2SO_4, H_2SO_4). The ether is easily removed by evaporation.

$$RCOONa + H_2SO_4 \xrightarrow[\text{Distill or extract}]{} RCOOH + NaHSO_4$$

Physical Properties. There is a gradual change in boiling point and solubility in water as we proceed from one member of the homologous series to the next higher straight-chain compound. The acids above butyric are only slightly soluble in water, and the solubility decreases as the hydrocarbon portions of the molecule become more predominant with the increase in the number of carbon atoms (cf. p. 73). The acids are all very soluble in alcohol, ether, benzene,

Name	*Formula*	*Boiling Point*	*Melting Point*	*Density at 20°*	*Solubility Grams per 100 Grams of Water at 20°*
Formic acid	$HCOOH$	101°	8°	1.220	Miscible in all proportions
Acetic acid	CH_3COOH	118°	17°	1.049	
Propionic acid	CH_3CH_2COOH	141°	−22°	0.992	
n-Butyric acid	$CH_3CH_2CH_2COOH$	164°	− 8°	0.959	
Isobutyric acid	$(CH_3)_2CHCOOH$	154°	−47°	0.949	20
n-Valeric	$CH_3CH_2CH_2CH_2COOH$	187°	−18°	0.942	4
n-Caproic	$CH_3CH_2CH_2CH_2CH_2COOH$	202°	− 1.5°	0.929	Less than 1
n-Heptoic	$CH_3(CH_2)_5COOH$	223°	−10°	0.918	Less than 1
Caprylic	$CH_3(CH_2)_6COOH$	237°	16°	0.914	Less than 1
n-Nonylic	$CH_3(CH_2)_7COOH$	253°	12.5°		Practically insoluble
Capric	$CH_3(CH_2)_8COOH$	268°	31°		
Undecylic	$CH_3(CH_2)_9COOH$		28.5°		
Lauric	$CH_3(CH_2)_{10}COOH$		43°		
Tridecylic	$CH_3(CH_2)_{11}COOH$		42.5°		
Myristic	$CH_3(CH_2)_{12}COOH$		53.8°		
Pentadecylic	$CH_3(CH_2)_{13}COOH$		53°		
Palmitic	$CH_3(CH_2)_{14}COOH$		64°		
Margaric	$CH_3(CH_2)_{15}COOH$		61°		
Stearic	$CH_3(CH_2)_{16}COOH$		69°		

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and chloroform and even the lower members may be extracted from their water solutions by the last three solvents.

Some of the physical properties of the series are given on p. 76.

It will be noted that the melting points of the straight-chain acids show no regular increase but vary up and down; the melting point of the acids containing an even number of carbon atoms is higher than the preceding one in the series. The straight-chain acid with a total of nine carbon atoms melts at 12.5°, and all those above this are solid at room temperature. The odor of the acids above propionic is very disagreeable unless they are so nonvolatile as to be practically odorless. Rancid butter owes its disagreeable smell to butyric acid.

Dissociation Constants. Those who are familiar with the quantitative aspects of the theory of electrolytic dissociation will recall that the strength of acids may be expressed in terms of a dissociation constant K_A which is defined as follows:

$$K_A = \text{conc. of hydrogen ion} \times \left(\frac{\text{conc. of acid ion}}{\text{conc. of undissoc. acid}}\right)$$

It is evident that, when the quotient inside the parentheses has a value of one, the value of K_A is equal to the concentration of the hydrogen ion. This condition is easily realized with weak acids by preparing a solution which contains one mole of the acid and one mole of a soluble salt of the acid. Since the free acid is only very slightly dissociated, the concentration of the undissociated acid is practically the same as the total concentration. The salt, on the other hand, is completely ionized and the concentration of the acid ion is therefore equal to the total concentration of the salt. Consequently, one may visualize the dissociation constant of a weak acid by thinking of it as being equal to the acidity (the hydrogen ion concentration) of a mixture of the acid and its soluble salt in equal molar amounts. The dissociation constants of some of the fatty acids are as follows:

$$\text{Formic, } K_A = 2.14 \times 10^{-4}$$

$$\text{Acetic, } K_A = 1.86 \times 10^{-5}$$

$$n\text{-Butyric, } K_A = 1.6 \times 10^{-5}$$

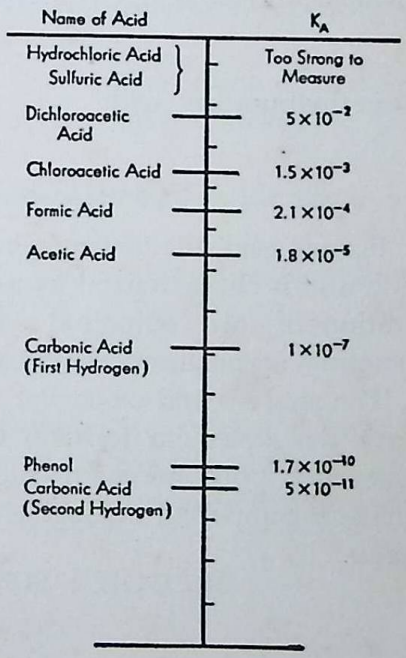

FIG. 4. The relative strengths of some common acids. The strongest acids are at the top of the scale; each scale unit corresponds to a ten-fold change in the acid dissociation constant.

It will be recalled that the hydrogen ion concentration of pure water $= 1 \times 10^{-7}$. The dissociation constants of the first and second hydrogens of carbonic acid are about

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1×10^{-7} and 5×10^{-11}, respectively. The diagram in Fig. 4 shows graphically the relative acidities of some common acids; several acids are included which will be considered later (phenol, p. 429, chloroacetic acid, p. 236).

Nomenclature. A great many of the fatty acids having a straight chain are found in nature, and were isolated before chemical nomenclature had been put on a rational basis; for this reason they have trivial names. In a systematic fashion, acids may be named as derivatives of acetic acid or by the Geneva system. The former method is illustrated by trimethylacetic acid, $(CH_3)_3CCOOH$. This is a convenient method for relatively simple acids.

In the Geneva system, the acid is named according to the longest chain of carbon atoms which it contains, *counting the carbon of the carboxyl group*. The suffix *-oic* is then added to the name of the paraffin hydrocarbon corresponding to this chain; branches are named and numbered as in the hydrocarbons. The numbering is always started *on* the carboxyl group. The following examples will make this method clear: pentanoic acid, $CH_3CH_2CH_2CH_2COOH$; $CH_3\underset{\underset{CH_3}{|}}{C}HCH_2COOH$, 3-methylbutanoic acid.

STRUCTURE OF ACETIC ACID

Formic acid, the first member of the series, occupies a unique position and is characterized by a number of special reactions. A consideration of this compound will be postponed, therefore, until we examine a typical representative of the entire class, namely *acetic acid*.

The analysis and molecular weight of acetic acid show that it must have the molecular formula $C_2H_4O_2$. Like the alcohols, the acids react with phosphorous trichloride yielding phosphorous acid and a halogen compound analogous to an alkyl halide, but called an *acyl halide*.

$$3RCOOH + PCl_3 \longrightarrow \underset{\substack{\text{An}\\\text{acyl}\\\text{chloride}}}{3RCOCl} + P(OH)_3$$

This reaction proves the presence of an hydroxyl group in the molecule. We can indicate this development in our knowledge by the provisional formula $(C_2H_3O)(OH)$. The next question is: How are the two carbon atoms and the oxygen atom joined?

The linkage $-C-C-O$ in the molecule rather than $C-O-C$

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is established by the following transformations which show that two carbon atoms are united in acetic acid.

1. Acetonitrile, CH_3CN, prepared from methyl iodide and potassium cyanide, yields acetic acid or its salts on boiling with an acid or alkali.

2. Ethyl alcohol on oxidation yields acetic acid.

3. By a series of reactions involving the acyl chloride C_2H_3OCl, it is possible to go back from acetic acid to acetonitrile; in another series of reactions one can reconvert acetic acid to ethyl alcohol.

To reconcile these facts with a formula in which the carbon atoms were linked through oxygen would require the popping in and out of an oxygen atom in a carbon chain in an extremely unlikely manner. When it is possible to go back and forth between two compounds, it is very likely that the structure of the carbon chain in the two is the same. The more ways this can be accomplished the more certain is the proof. This is a general principle basic to the establishment of the structural formulas of organic compounds. From these considerations we write the following skeleton of acetic acid as established with a high degree of probability, C – C – O – H.

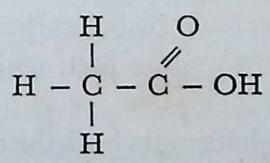
We have now an oxygen atom and three hydrogen atoms to account for. The presence of a methyl group in acetic acid is indicated by the following facts:

1. On heating sodium acetate with sodium hydroxide methane is formed.

2. Methylmagnesium iodide (p. 28) on treatment with carbon dioxide yields a salt of acetic acid.

$$CH_3MgI + CO_2 \longrightarrow CH_3COOMgI$$

These facts justify us in writing a formula with a methyl group; if that is done there is only one way to dispose of the remaining oxygen atom and to keep the valence of carbon four and oxygen two; namely as follows:



The Experimental Basis of Structural Formulas. It may be well to point out that the formulas of the simpler organic compounds are based on many different experimental facts, all of which are consistent

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with the structure ascribed. In discussing the structure of a substance in an elementary course, it is impossible to cite all the evidence. Therefore, only the most vital facts are given and the reasoning is based on them. As the science of organic chemistry grows, more complicated substances are constantly being investigated. At first, any structural formula rests on only a relatively few experimental facts, and is necessarily tentative; if need be, it is changed when more is known about the substance. Finally, the accumulation of evidence is so great that the formula is generally accepted. Strictly speaking, no structural formula can be said to be proved (with the exception, perhaps, of such simple substances as methane and methyl alcohol). The structure of most of the compounds dealt with in this book may be said to have been demonstrated "beyond a reasonable doubt." If, however, tomorrow some investigator should discover an experimental fact clearly inconsistent with an accepted formula, this would reopen the subject for discussion and experimentation.

THE STRUCTURE OF THE CARBOXYL GROUP

The structure of acetic acid just established locates the arrangement of the nuclei of the atoms in the molecule. It says nothing about the way these nuclei are joined. The experimental facts cited and the reasoning used, which are characteristic of organic chemistry, are not concerned with the arrangement of the electrons. To be sure, in making the statement that to keep the valence of carbon four and oxygen two we write a double bond between one oxygen and carbon, we make certain assumptions about valence bonds or the electrons they represent. But it is only through physical rather than chemical evidence that we can establish accurately the arrangement of electrons. This evidence has only become available in recent years and only recently have theoretical ways of handling it been developed.

Resonance of the Carboxyl Group. We can imagine the following distributions of the electrons in the carboxyl group of acetic acid. The electronic formulas are written first, with an equivalent formula as shown on page 81.

It will be seen that in each formula both the carbon and oxygen atoms have octets. No other electronic arrangement meets this requirement. The first (I) corresponds to the formula we have already written for the carboxyl group; in II the two oxygen atoms are said to have formal charges because one has an electron more, the other an electron less

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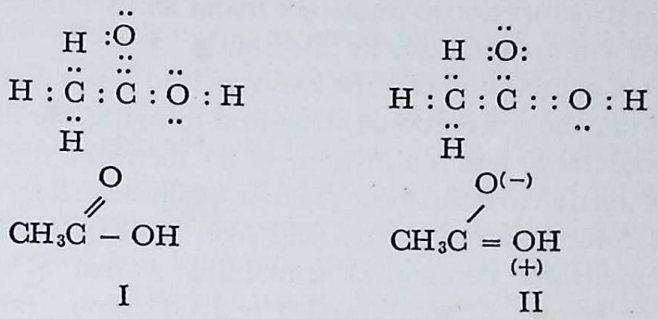
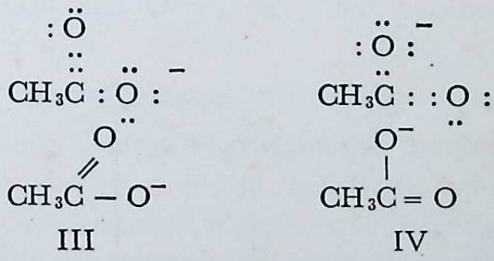
than the six which surround the nucleus in the neutral atom. If stable compounds existed corresponding to formulas I and II they would be isomeric only with respect to the arrangement of electrons. No such isomers are found in organic chemistry, as has already been



I II

stated in considering the electronic structures of butadiene (p. 70). Instead we have evidence to indicate that the compound in question partakes of both structures and is said to be a *resonance hybrid*. Or we may say that in a carboxyl group there is resonance between formulas I and II.

Resonance of the Ion. We can write two resonating structures for the ion of acetic acid (the acetate ion). The electronic structure of the methyl group is omitted in the formulas.



III IV

Here, unlike the resonance forms of butadiene or the carboxyl group, the two arrangements of the electrons do not correspond to imaginable electromers (isomers with different electronic structures). The symmetry of the carboxyl ion is such that even if there were two stable ions represented by III and IV, their properties would be identical, and the salts containing these ions would be homogeneous substances. Actually, however, the ions are resonance hybrids and partake of the two structures even more than do the hybrids of butadiene or the free acid. Indeed, it is a general principle that the more similar the two resonance structures the less a formula representing one of the two is a correct representation.

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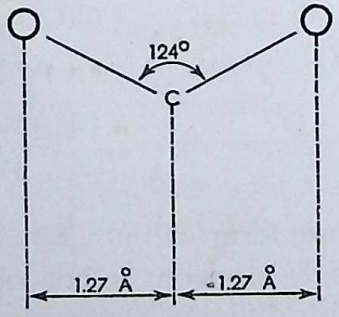
Resonance Energy. Whenever there is a possibility of resonance between two electronic structures and the real arrangement of the electrons is that of a resonance hybrid between the two forms, the compound is more stable than it would otherwise be. This increased stability of a structure due to resonance manifests itself in several ways, of which we will mention two at this time.

The heat of combustion of a resonance hybrid is less than would be predicted from the conventional structural formula; the difference is called *resonance energy* and is a measure of the increased stability of the molecule or ion due to resonance. This can be illustrated by comparing the heat of combustion of a fatty acid such as $CH_3CH_2CH_2COOH$ with a four-carbon compound containing a real C =O group (aldehyde or ketone, Chap. 7) and a real OH group (an alcohol). This difference is found to be about 20 kg-cal per mole.

A consequence of the greater stability of the compounds which show some measure of resonance is the closer approach of the nuclei of the atoms involved in the resonating structures. For example, the usual interatomic distances between carbon and oxygen are for a single link (as in CH_3OCH_3) 1.42 Å, for a double link (as in an aldehyde) 1.21 Å. In the ion of the fatty acids the *two oxygen atoms are at the same distance from the carbon atom;* this distance is 1.27 Å. Or, the difference between that predicted for O = C − O and observed is $1.42 + 1.21 - 2 \times 1.27 = .09$ Å.



Arrangement of carbon and oxygen atoms in anion of carboxyl group.

Dimeric Forms and the Hydrogen Bond. Determination of the density of the vapor of the aliphatic acids shows that below 200° to 300° at one atmosphere pressure the molecules are for the most part doubled. The equilibrium between the single (monomeric form) and double molecules (dimeric form) is attained almost instantaneously without any catalyst. This fact alone indicates that we are dealing with some type of linkage more akin to the intermolecular forces in

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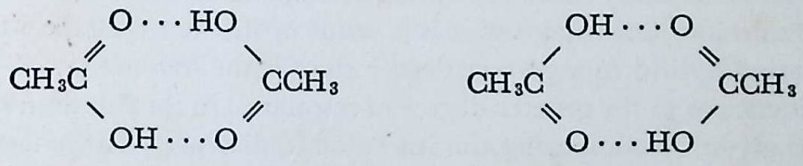
liquids than to the usual covalent bond.

$$(CH_3COOH)_2 \rightleftharpoons 2CH_3COOH$$

Equilibrium established instantaneously. Degree of dissociation depends on temperature and pressure.

Likewise in some solvents the molecular weight of the fatty acids corresponds to a double molecule. Abnormal molecular weights under certain circumstances are not unusual in organic chemistry and the phenomenon is usually referred to as *association*. It is particularly common in compounds containing hydroxyl groups and carboxyl groups, and this fact among others has led chemists in recent years to postulate the existence of a weak link involving the hydrogen atom. The exact formulation of the hydrogen bond in terms of the electronic theory of valence is still a matter of discussion. The fact that such a link does occur, however, is now generally recognized and explains a number of otherwise peculiar phenomena in various types of organic compounds. The dimeric forms of the acids may be represented by the following formulas in which there is a possibility of resonance of the type represented by the structures written for the carboxyl group.



Possible resonating structures of dimeric forms of acetic acid

Hydrogen bonds are likewise responsible for the association of water and alcohol molecules which is reflected in the high boiling points of these compounds as compared with the ethers. The dotted line in the formulas above is a pure convention since the electronic distribution between the two oxygen atoms and the hydrogen is still unsettled. Electron diffraction has shown that the distance here is much greater than in a covalent bond (2.7 Å).

Acid Strength. The hydrogen atom of the carboxyl group can be replaced by a metal to form salts like sodium acetate which, in water, dissociates into ions, Na^+ and CH_3COO^-. The hydrogen atom of ethyl alcohol can likewise be replaced by sodium. This cannot be done, however, with sodium hydroxide in a neutralization reaction like that with acetic acid, but requires the use of sodium. On solution in water, sodium ethoxide is practically completely hydrolyzed.

$$C_2H_5ONa + H_2O \longrightarrow C_2H_5OH + NaOH$$

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It is common practice to distinguish between those hydrogen compounds whose metallic derivatives are only slightly hydrolyzed in aqueous solution and those which are essentially completely hydrolyzed. We speak of the former as acids; the latter, the alcohols, as neutral substances. The difference is one of degree, however, and it would be more accurate to speak of all hydroxyl compounds as acids. As a matter of convenience we shall stick to the conventional practice and distinguish between alcohols and acids, meaning by the latter term acids stronger than water.

Why is the hydrogen atom in a carboxyl group so much more acidic than in the hydroxyl group of an alcohol? In both substances the hydrogen compound, through electrostatic attraction and hydrogen bonding, forms loose compounds with water molecules. (So too does the hydrogen ion itself.) The difference seems to rest not so much in the hydrogen compound as in the ion. The resonance of the ion is greater than that of the acid because the two resonance structures are identical in the former and not in the latter. Therefore, the resonance energy of the ion is greater than of the acid. This is probably the chief reason why the fatty acids are strong enough to be classed as acids in water solution. One may say it is a result of the fact that the ion is a resonating hybrid to a greater degree than is the free acid.

Evidence as to the greater degree of resonance in the ion than in the acid is given by comparing the interatomic distances. In the ion the C — O bond is 1.27 Å. In the monomer of formic or acetic acid, however, the C = O and C — OH distances are very nearly the same as they are in simple compounds without resonance. This indicates that, although there is considerable resonance in the free acid as shown by the energy measurements, there is more resonance in the ion. It may be noted that in the dimer, however, there is some shortening of the C — O distance due to resonance involving the dimeric structures given on page 83.

INDUSTRIAL PREPARATION AND USES OF THE FATTY ACIDS

Formic acid is prepared industrially from sodium formate, which in turn is prepared by heating sodium hydroxide and carbon monoxide (from water gas).

$$CO + NaOH \xrightarrow[\text{6–10 atm}]{200^\circ} HCOONa$$

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To prepare the acid, the salt is heated carefully with the calculated amount of sulfuric acid. If formic acid itself is heated with sulfuric acid it undergoes dehydration; the reaction is a convenient laboratory source of carbon monoxide.

$$HCOOH \xrightarrow[H_2SO_4]{60°-80°} H_2O + CO$$

Formic acid is stronger than the other aliphatic acids (cf. Fig. 4, p. 77); and, unlike the other aliphatic acids, it is readily oxidized.

$$HCOOH + [O] \longrightarrow H_2O + CO_2$$

Because of these two properties it finds considerable use in industrial operations, particularly in the textile industry.

Acetic acid is obtained as a dilute aqueous solution, vinegar, by the fermentation of weak aqueous solutions of alcohol. The anhydrous acid, known as *glacial acetic acid* because of its high melting point, 16.6°, is not prepared by concentrating vinegar but by a variety of industrial processes described in Chap. 8. The acid is widely used in industry when a weak acid is required, and its esters are extensively used as solvents. Acetic acid is one of the important chemicals of commerce; the total production, synthetic and recovered, in 1944 was over 800,000,000 lb.

The higher aliphatic acids with even numbers of carbon atoms are obtained from the naturally occurring fats and oils. Their preparation and uses are considered in Chap. 10.

GENERAL METHODS OF PREPARING ACIDS

The important members of the fatty acid series are prepared industrially by special methods or from special sources. When we wish to prepare any of the other fatty acids in the laboratory we use an alcohol as our starting point.

Oxidation of a Primary Alcohol. If we have a primary alcohol with the same number of carbon atoms, the problem is easy. The oxidation of a primary alcohol yields an acid with the same number of carbon atoms.

$$RCH_2OH + 2[O] \longrightarrow RCOOH + H_2O$$

An illustration of this is the oxidation of ethyl alcohol by air in the presence of "mother of vinegar." In the laboratory a mixture of potassium dichromate and sulfuric acid is often employed as the

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oxidizing agent. Under certain conditions an intermediate product, an aldehyde (Chap. 7), may be isolated, but if the process is so arranged that this compound remains in contact with the oxidizing agent it is further oxidized to the acid. The simple organic acids themselves are not readily oxidized, so that there is little danger of carrying the process too far.

$$CH_3CH_2OH + 2[O] \xrightarrow{K_2Cr_2O_7} CH_3COOH + H_2O$$

It will be noted that RCH_2OH is a general formula for any primary alcohol and RCOOH for the corresponding acid. The alcohol which corresponds to formic acid, HCOOH, is methyl alcohol, CH_3OH.

Acids from Lower Alcohols. If we have the problem of preparing an acid with one more carbon atom than the alcohol at hand, a simple oxidation will not avail. There are two ways of accomplishing this synthesis, however. Both start with the alkyl halide RX and yield the same acid RCOOH. They are illustrated below by the synthesis of propionic acid from ethyl bromide.

1. **Grignard Synthesis of Acids.** In this process dry carbon dioxide is passed into the ethereal solution of the Grignard reagent, or the Grignard reagent is poured onto dry ice. Then the reaction mixture is decomposed with dilute hydrochloric or sulfuric acid which sets free the organic acid.

$$CH_3CH_2Br + Mg \xrightarrow[\text{ether}]{\text{Dry}} CH_3CH_2MgBr$$

$$CH_3CH_2MgBr + CO_2 \longrightarrow CH_3CH_2COOMgBr$$

$$CH_3CH_2COOMgBr + HCl \longrightarrow CH_3CH_2COOH + MgBrCl$$

The organic acid is extracted with ether and is obtained by evaporating this solvent. This process is a good laboratory method of preparing many acids and has been widely employed since the discovery of the Grignard reaction.

2. **Nitrile Synthesis of Acids.** The older process of preparing acids involves the preparation of a **nitrile,** RCN. This substance has the carbon atom of the cyanide group directly bound to the alkyl group. It is an organic cyanide and may be regarded as an ester of hydrocyanic acid. The nitriles are formed by boiling an alcoholic solution of the alkyl halide with sodium cyanide (p. 24).

$$C_2H_5Br + NaCN \longrightarrow C_2H_5CN + NaBr$$

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The nitriles are hydrolyzed on boiling with dilute alkalies.

$$CH_3CH_2CN + NaOH + H_2O \xrightarrow{\text{Boil}} CH_3CH_2COONa + NH_3$$

The product is the sodium salt; from the water solution of the salt the free acid may be prepared by acidification with a mineral acid and extraction with ether.

$$CH_3CH_2COONa + HCl \longrightarrow CH_3CH_2COOH + NaCl$$

The hydrolysis of nitriles to acids may also be accomplished with strong mineral acids.

$$CH_3CH_2CN + H_2SO_4 + 2H_2O \longrightarrow CH_3CH_2COOH + NH_4HSO_4$$

SOME GENERAL REACTIONS OF ACIDS

The acidic reaction of the carboxyl group is perhaps the most characteristic property of organic acids. Certain other reactions, however, are important. They are illustrated by the following general equations, where RCOOH stands for acetic acid or a higher homolog.

1. Replacement of OH by halogen; formation of acid chlorides.

$$3RCOOH + PCl_3 \longrightarrow 3RCOCl + P(OH)_3$$

This reaction has already been mentioned in the discussion of the structure of acetic acid.

2. Replacement of OH by OR; formation of esters.

$$RCO\,\vdots\,OH + H\,\vdots\,OR \rightleftarrows RCOOR + H_2O$$

Two other reactions of much less importance may be mentioned. In both the carboxyl group is eliminated as carbon dioxide.

3. Formation of a paraffin hydrocarbon RH.

$$RCOONa + NaOH \xrightarrow[300^\circ]{\text{Fused}} RH + Na_2CO_3$$

$$\text{e.g.,}\quad CH_3COONa + NaOH \longrightarrow CH_4 + Na_2CO_3$$

4. Formation of a hydrocarbon RR by electrolysis of the sodium salt, RCOONa.

$$2RCOO'(\text{minus two electrons at anode}) \longrightarrow RR + 2CO_2$$

$$\text{e.g.,}\quad 2CH_3COO' \longrightarrow CH_3CH_3 + 2CO_2 + 2\text{ electrons}$$

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ACID CHLORIDES

When an acid is treated with phosphorus trichloride (PCl_3), the OH group of the carboxyl group is replaced by chlorine. Phosphorus pentachloride and thionyl chloride ($SOCl_2$) are also used in replacing the OH group of acids. The action of the latter is illustrated by the equation:

$$CH_3\overset{\overset{O}{//}}{C} - OH + SOCl_2 \longrightarrow CH_3\overset{\overset{O}{//}}{C} - Cl + HCl + SO_2$$

An acid chloride is also called an *acyl chloride*. It has the general formula RCOCl, and is named by slightly changing the name of the acid; thus, acet-yl chloride and propion-yl chloride. Formyl chloride, HCOCl, is unknown; attempts to prepare it yield only hydrogen chloride and carbon monoxide. Acid bromides and acid iodides are known but are of no importance. The boiling points of the lower acyl chlorides are given in the table below.

Name	*Formula*	*Boiling Point*
Acetyl chloride	CH_3COCl	52°
Propionyl chloride	CH_3CH_2COCl	80°
Butyryl chloride	$CH_3CH_2CH_2COCl$	102°

These substances are all very irritating to the mucous membrane, and fume in moist air.

Reactions of Acid Chlorides. Acyl chlorides are much more reactive than alkyl halides. Acetyl chloride reacts violently with water, alcohol, and ammonia at room temperature.

Hydrolysis $CH_3COCl + H_2O \longrightarrow CH_3COOH + HCl$

Alcoholysis $CH_3COCl + C_2H_5OH \longrightarrow CH_3COOC_2H_5 + HCl$

Ammonolysis $CH_3COCl + 2NH_3 \longrightarrow CH_3CONH_2 + NH_4Cl$

The product of the second reaction is an **ester;** the substance formed in the last reaction is an **amide.** These reactions show how the acid chlorides are useful in preparing other compounds.

The characteristic reactions of acyl chlorides are all replacement reactions in which the halogen atom is replaced by a group of atoms. With the acid chlorides of the simpler acids these reactions occur very rapidly at room temperature, in fact often with almost explosive violence. This behavior of the *acyl* chlorides is in marked con-

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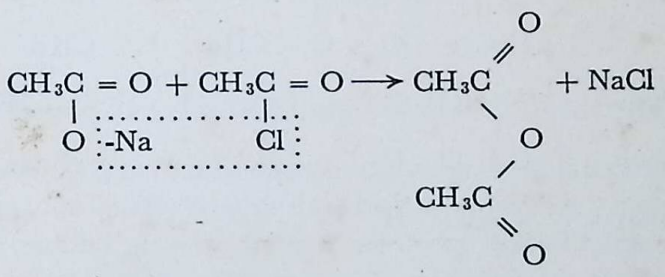
trast to that of the alkyl halides such as ethyl chloride. The alkyl chlorides can be boiled with water and alcohol without any appreciable reaction; in order to replace the halogen with hydroxyl in these compounds, silver hydroxide or an alkali is necessary. The speed of the reaction between an acid chloride and an alcohol depends on the structure of both. Acetyl chloride is more rapid in its reactions than the higher homologs, and primary alcohols interact faster with a given acid chloride than do secondary or tertiary. In this reaction it will be noted that the hydrogen atom of the alcohol is being replaced just as in the formation of alkoxides with metallic sodium, and just as in that reaction, the primary alcohols are the most reactive, secondary next, and tertiary least. When it is a matter of replacing the *hydroxyl* group of the alcohols, however, as in the formation of alkyl halides, the situation is just reversed, and the tertiary alcohols are the most rapid in their action (p. 27).

ACID ANHYDRIDES

When anhydrous sodium acetate and acetyl chloride are heated together, a reaction takes place and **acetic anhydride,** $(CH_3CO)_2O$ is formed.



This compound is a representative of the acid anhydrides $RC(=O)-O-C(=O)-R$ or $(RCO)_2O$. The acid anhydrides are formally related to acids as the ethers are to alcohols. There is little resemblance in properties, however, between the two classes. The anhydride of formic acid is unknown; all attempts to prepare it yield carbon monoxide. As the name indicates, the anhydrides react with water, regenerating acids; they also react with alcohols forming esters.

$$(RCO)_2O + H_2O \longrightarrow 2RCOOH$$

$$(CH_3CO)_2O + C_2H_5OH \longrightarrow CH_3COOC_2H_5 + CH_3COOH$$

Acetic Anhydride. Acetic anhydride is prepared in the laboratory from sodium acetate and acetyl chloride. Industrially it is made by the action of sulfur chloride (S_2Cl_2) on acetic acid or sodium acetate, and by heating acetic acid vapor to very high temperatures

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in the presence of a catalyst under special conditions whereby provision is made for removing the water formed in the process.

Acetic anhydride is a liquid boiling at 140°; it has a very irritating odor. Its importance depends on the fact that it reacts with many substances forming acetyl derivatives, that is, compounds containing the acetyl group CH_3CO-. Large quantities of acetic anhydride are manufactured for the production of cellulose acetate, one of the artificial silks now widely used (p. 299). During 1935 over 116,000,000 lb. of acetic anhydride was produced; in 1944 the production had increased to 495,000,000 lb.

Acetylating Agents. Acetyl chloride and acetic anhydride are spoken of as *acetylating agents* because they will react with many substances having an active hydrogen atom to form acetyl derivatives. This is illustrated by the following diagram of the reactions with water, alcohol, and ammonia.

	$CH_3\overset{\overset{O}{\|}}{C}-$	$O-\overset{\overset{O}{\|}}{C}-CH_3$	$CH_3\overset{\overset{O}{\|}}{C}-$	Cl
Hydrolysis	HO	H	HO	H
Alcoholysis	C_2H_5O	H	C_2H_5O	H
Ammonolysis	NH_2	H	NH_2	H

ACYL GROUPS AND ALKYL GROUPS

The acyl group RCO− may be regarded as the hypothetical group formed from an acid by removal of the OH group. The acyl groups

Compounds Having an Alkyl Group		*Compounds Having an Acyl Group*	
Class Name	*General Formula*	*Class Name*	*General Formula*
Alcohol	ROH	Acid	$R\overset{\overset{O}{//}}{C}-OH$
Alkyl chloride	RCl	Acyl chloride	$R\overset{\overset{O}{//}}{C}-Cl$
Ether	ROR	Acid anhydride	$R\overset{\overset{O}{//}}{C}-O-\overset{\overset{O}{//}}{C}-R$

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should not be confused with the acid ion $RCOO^-$. For example, the acetyl group $CH_3\overset{\overset{O}{//}}{C}-$ is quite different from the acetate ion CH_3COO^-.

The table on page 90 may serve as a general review of some of the types of compounds thus far studied. The contrast between the *acyl* and corresponding *alkyl* compounds should be carefully studied; they bear a formal resemblance to each other, but their chemical and physical properties are very different.

ESTERS OF ORGANIC ACIDS

Esterification. When an alcohol and an acid are brought together, the hydroxyl group of the acid and the hydrogen atom of the alcohol unite to form water: the new compound is called an *ester*. The reaction is known as *esterification*. It may be illustrated by the formation of ethyl acetate from acetic acid and ethyl alcohol.

$$CH_3COOH + C_2H_5OH \rightleftharpoons CH_3\overset{\overset{O}{//}}{C} - OC_2H_5 + H_2O$$

The reaction does not go to completion, and, at room temperature in the absence of a catalyst, equilibrium is attained very slowly. Therefore, it is common practice to heat the mixture to the boiling point of the alcohol and to add a little sulfuric acid or hydrochloric acid as a catalyst. Another method of accomplishing the same end is to heat the alcohol with equivalent quantities of sulfuric acid and the sodium salt of the acid. The sulfuric acid fulfills two functions: that of liberating the organic acid from the salt, and catalyzing the reaction.

$$RCOONa + R'OH + H_2SO_4 \rightleftharpoons R\overset{\overset{O}{//}}{C} - OR' + NaHSO_4 + H_2O$$

The esters of organic acids except formic have the general formula $R\overset{\overset{O}{//}}{C} - OR'$ ($RCOOR'$) where R and R′ may be the same or different alkyl groups; the esters of formic acid have the general formula HCOOR. There is, therefore, an homologous series for each acid, the alkyl groups becoming increasingly larger. Thus, we have methyl formate, $HCOOCH_3$; ethyl formate, $HCOOC_2H_5$; propyl formate,

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$HCOOC_3H_7$ (two isomers), etc. Similar series may be written with acetic acid, propionic acid, and all the other fatty acids.

In the following table are listed some of the commoner esters which can be prepared from the alcohols and acids already considered. They are all liquids which float on water.

The esters have a very pleasant, fruity odor, each different from that of the others. It is particularly interesting that although butyric and valeric acids have very disagreeable odors, their esters are sweet-smelling substances. The characteristic fragrance of many fruits and flowers is due to the presence of various esters. Thus, amyl acetate, $CH_3COOC_5H_{11}$, has a pear-like odor and the odor of methyl butyrate, $C_3H_7COOCH_3$, is reminiscent of pineapple. A number of the

SOME COMMON ESTERS

Name	*Formula*	*Boiling Point*
Methyl formate	$HCOOCH_3$	32°
Ethyl formate	$HCOOCH_2CH_3$	54°
Methyl acetate	CH_3COOCH_3	57°
Ethyl acetate	$CH_3COOCH_2CH_3$	77°
n-Butyl acetate	$CH_3COOCH_2CH_2CH_2CH_3$	127°
n-Amyl acetate	$CH_3COOCH_2CH_2CH_2CH_2CH_3$	148°
Isoamyl acetate	$CH_3COOCH_2CH_2CH(CH_3)_2$	143°
Methyl propionate	$CH_3CH_2COOCH_3$	80°
Ethyl propionate	$CH_3CH_2COOCH_2CH_3$	99°

simple esters are manufactured for use in artificial perfumes and flavors. The most important use of esters is as solvents, especially in the manufacture of quick-drying automobile lacquers (p. 298).

The fats and oils which occur in animals and plants are esters of an alcohol with three hydroxyl groups and acids of high molecular weight. They are of great importance, not only as food, but as the raw material used in manufacturing soap, candle stock, and glycerine (Chap. 10).

Other Methods of Preparing Esters. In addition to the esterification of acids, esters may also be prepared by (1) the reaction between an acid chloride and an alcohol (p. 88); (2) the reaction between an acid anhydride and an alcohol (p. 89); and the reaction between the silver salt of an acid and an alkyl halide.

$$CH_3COOAg + C_2H_5Br \longrightarrow CH_3COOC_2H_5 + AgBr$$

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The vinyl esters of the fatty acids are prepared by the addition of the acid to acetylene, the vinylation reaction mentioned earlier on page 67. The zinc or cadmium salt of the acid being added is used as a catalyst.

$$CH_3COOH + CH \equiv CH \xrightarrow{(CH_3COO)_2Zn} CH_3COOCH = CH_2$$

Esterification and Hydrolysis. An Equilibrium. The interaction of an alcohol and acid does not go to completion as do many organic reactions. If we start with 1 mole of acetic acid (60 g) and 1 mole of ethyl alcohol (46 g), we find that, try as we will, we cannot get a reaction mixture containing more than about 66 per cent of 1 mole of ethyl acetate. On the other hand, if we were to start with ethyl acetate and heat it with 1 mole of water for a long time, we would find that the reaction apparently stopped when the mixure contained about 66 per cent of unchanged ester. Thus, whether we start with alcohol and acid or with water and ester, *the final composition of the reaction mixture is the same.* This state of affairs is typical of a reversible reaction. The reverse of esterification is called *hydrolysis.*

The Composition of the Equilibrium Mixture. The composition of the final reaction mixture, the equilibrium mixture, is approximately expressed by what is often called the *mass law*. This is given by the following equation in which the symbols [ester], [H_2O], etc., refer to concentrations expressed as moles per liter, or better as mole fractions.

$$\frac{[\text{Ester}] \times [H_2O]}{[\text{Alcohol}] \times [\text{Acid}]} = K \text{ (the equilibrium constant)}$$

For example, in the preparation of ethyl acetate, experiments show that the equilibrium mixture contains about 0.6 mole of ester, if we start with one mole of acid and one of alcohol (a total of 2 moles). Therefore, the mole fraction of ester is $\frac{0.6}{2} = 0.3$ and of water the same (for each molecule of ester formed, one of water is also formed). The concentrations of alcohol and acid are $\frac{0.4}{2} = 0.2$ each. These numbers substituted in the equation give:

$$\frac{0.3 \times 0.3}{0.2 \times 0.2} = 2.25 = K$$

Experiment shows that whatever relative amounts of acetic acid and ethyl alcohol are employed, the composition of the equilibrium mixture is such that K has *approximately* this value.

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Practical Applications of the Mass Law. It is an easy matter to calculate the composition of an equilibrium mixture if we know the value of K and the relative amounts of alcohol and acid at the start. Without going through the calculations, it is evident from an inspection of the mass law equation that if we use a large excess of alcohol, the yield of ester per mole of acid will be increased. For this reason, if we wish to prepare the ethyl ester of an expensive acid we use a considerable excess of the alcohol.

It is also evident that if we remove a certain amount of one of the products (water or ester), a further amount will be formed so that the composition of the mixture will conform to the mass law expression. This can be realized very often in practice and is sometimes referred to as *upsetting the equilibrium*. For example, if the alcohol, ester, and acid boil much higher than water, it is often possible to distill the latter from the reaction mixture. This is also accomplished by making use of an azeotropic mixture (p. 15). Some solvent such as benzene is added to the acid and alcohol. On distillation at a relatively low temperature, a mixture of water and benzene is separated from the reaction mixture. In this way the yield of the process may be much greater than otherwise would be possible. It should be noted that these methods are only effective if they are carried out under such conditions (temperature and catalyst) that the rate of the reactions is rapid and more product will be rapidly formed as some is removed.

Reaction Rates and Equilibria. We have already met three examples of reversible reactions where equilibrium mixtures containing appreciable quantities of products and reactants are formed. They are:

1. The isomerization of butane to isobutane (p. 41).
2. The dissociation of the dimeric acid molecules in the vapor (p. 82).
3. The reaction between liquid acids and alcohols (esterification) just considered.

Probably the student has also studied reversible reactions and the application of the mass law to them in the ionic reactions of inorganic chemistry. If so he is accustomed to thinking that equilibria are established very rapidly if not instantaneously. This is true when the reaction involves ions alone. It is also true in case 2 above, the dissociation and association of formic or acetic acid molecules. But this is the exception in organic chemistry. Here a very special and weak hydrogen bond is involved. The much more usual situation in organic

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chemistry is illustrated by examples 1 and 3, the isomerization of butane and esterification. Here the reactions in both directions are very slow under ordinary conditions and require a catalyst.

The factors affecting the rate of a reaction must not be confused with the factors affecting the composition of the equilibrium mixture. Whether we are considering the forward or back reaction of a reversible reaction, or a reaction which runs to completion, we find that a rise of temperature always increases the rate. (As a general rule the rate of reactions involving liquids or solutions approximately doubles with every 10° increase.) We further find that it is almost always possible to increase the rate by the use of some catalyst. And finally we know that increasing the concentration of the reactants (other factors being constant) increases the rate.

On the other hand the **composition of the equilibrium mixture is not affected by the absence or presence of a catalyst.** Thus we may speed up enormously the time in which equilibrium conditions are attained by finding the right catalyst, but *at constant temperature* we cannot shift the equilibrium by virtue of any catalyst.

The effect of changing concentration on the composition of the equilibrium mixture is governed by the mass law. An interesting example is afforded by a consideration of the dissociation of the dimeric acid molecules, example 2 above. Since equilibrium conditions are established almost instantaneously, the vapor density at different temperatures and pressures is automatically a measure of the composition of the equilibrium mixture. Since there are two molecules on the right of the equation and one on the left, diminishing the total pressure shifts the equilibrium to the right. (Not the value of the equilibrium constant, note, which is constant at a given temperature; but the relation of the concentration (or pressure) of the reactants and the products.) For example, a little above the boiling point acetic acid vapor at 1 atmosphere (760 mm) pressure has the composition corresponding to 50 per cent dissociation, while at 50 mm pressure and the same temperature it is 90 per cent dissociated.

The effect of changing temperature on the composition of the equilibrium mixture differs from one class of reaction to another. It is closely related to the heat change in the reaction. In the dissociation of acetic acid a rise of temperature greatly increases the degree of dissociation at a given pressure. This is usual in dissociation reactions $AB \longrightarrow A + B$. In these reactions heat is absorbed; in the reverse reaction (combination) heat is evolved. Increasing the temperature of acetic acid vapor by 12° increases the equilibrium constant by about tenfold; the heat absorbed in the dissociation is about 10 kg-cal. This is an endothermic reaction, but it does not run to completion at room

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temperature; it is a balanced reaction. The heat change in the isomerization of butane to isobutane, however, is much less (1.7 kg-cal), and heat is evolved in the conversion of butane to isobutane. Therefore increasing the temperature 400° (from 300° to 700°) has a relatively small effect and is in the direction of decreasing the equilibrium constant (by about a factor of 8). Finally in esterification, as in isomerization, very small amounts of heat are evolved or absorbed; indeed the heat change is so small that no accurate measurements are available. Corresponding to this we find the value of K is constant over the temperature range accessible for study of this reaction (a few hundred degrees).

In practice the organic chemist usually is not able to operate over a very wide temperature range. Most of his reactions involve solutions. He is limited, therefore, to the range between the freezing point and the boiling point of the solvent. To be sure, by working under pressure he can raise the boiling point, but in the laboratory this is somewhat inconvenient; and even in the industrial plants there are limits to the pressures and temperatures to which liquids can be heated. But the most serious limitation on raising the temperature of organic reactions is the fact that the majority of complex organic molecules begin to undergo a variety of decomposition reactions when temperatures approaching red heat are reached; many of them char as does sugar when dropped on a stove. The hydrocarbons are unusual in this respect, and in their industrial transformations larger temperature ranges can be employed than are usual in organic chemistry.

Mechanism of Esterification and Hydrolysis. It is obvious that two schematic representations of the esterification reaction may be written depending upon whether the acid or the alcohol loses an hydroxyl group. The water formed during esterification must arise from one of the following paths:

$$RCO \vdots OH + H \vdots OC_2H_5 \quad \text{or} \quad RCOO \vdots H + HO \vdots C_2H_5$$

The first mechanism was shown to be correct by esterifying an organic acid with methyl alcohol containing an abnormal amount of the heavy oxygen isotope (atomic weight, 18). The water obtained from this experiment had the normal density, showing that the oxygen atoms in the water were a mixture of the isotopes in the usual normal manner. This in turn proved that the oxygen in the water did not originate from the alcohol but rather from the acid; thus:

$$RCO \vdots OH + H \vdots OC_2H_5 \longrightarrow RCOOC_2H_5 + H_2O$$

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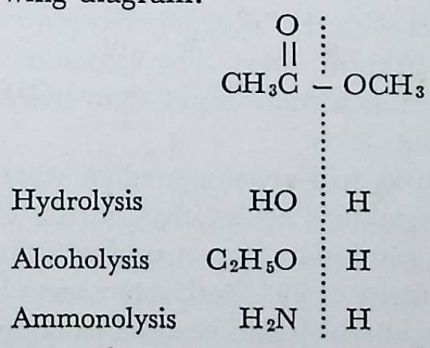
This is an illustration of how it is sometimes possible to establish the mechanism of a reaction by "tagging" one of the atoms.

Saponification of Esters. If we heat an ester with water, the hydrolysis is slow unless an acid or base is present to accelerate the process. In the absence of an acid or base, the reaction eventually reaches an equilibrium, and only about a third of the ester is hydrolyzed. If an equivalent amount of base is employed, however, the acid formed is neutralized and hence removed from the equilibrium. The process thus goes to completion. It is a special instance of hydrolysis and is called *saponification.*

$$CH_3COOC_2H_5 + NaOH \longrightarrow CH_3COONa + C_2H_5OH$$

Rates of Esterification and Hydrolysis. It has been found that the rate of formation of esters (under given conditions) depends on the structure of the acid and alcohol. Primary alcohols react most rapidly, tertiary least rapidly, with secondary in between. It will be noted this is the *reverse* of the order met with in alkyl halide formation; this is explained by the fact that in alkyl halide formation the hydroxyl of the alcohol is necessarily involved and in esterification the hydroxyl of the acid is eliminated (as demonstrated above). It is often difficult to esterify tertiary alcohols by the direct method. Acids of the general formula R_3CCOOH are also difficult to esterify directly. In general, branching the chain next to the carboxyl group causes the acid to esterify more slowly. Branching the chain of the alcohol has the same effect. The value of the equilibrium constant is relatively little affected by changes in the structure of the alcohol and acid. In esterification and hydrolysis, rates rather than energy changes determine the characteristic chemical behavior of alcohols and acids.

Reactions of Esters with Alcohols and Ammonia. Like the acid chlorides and acid anhydrides, the esters can undergo alcoholysis and ammonolysis as well as hydrolysis. This is illustrated with methyl acetate in the following diagram:



The reaction with ammonia is a method of preparing amides (p. 178). The alcoholysis reaction is also known as *ester interchange*. It takes place extremely slowly in the absence of a catalyst but very rapidly if a

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trace of sodium alkoxide is added to the mixture. The reaction does not go to practical completion unless there is a very large excess of one of the alcohols, or unless some provision is made for removing one of the products.

$$RCOOR' + R''OH \rightleftharpoons RCOOR'' + R'OH$$

Reduction of Esters to Alcohols. Esters are reduced to primary alcohols in good yields by the action of sodium and alcohol or by sodium and moist ether. The following equation for the preparation of *n*-hexyl alcohol from the ethyl ester of *n*-caproic acid illustrates the method.

$$CH_3(CH_2)_4COOC_2H_5 + 4[H] \xrightarrow{Na + C_2H_5OH} CH_3(CH_2)_4CH_2OH + C_2H_5OH$$

Esters may also be reduced catalytically with excellent results. The ester is shaken with hydrogen at elevated temperature and high pressure in the presence of a mixed catalyst of copper and chromium oxide (copper chromite).

$$RCH_2COOC_2H_5 + 2H_2 \xrightarrow[250°]{\text{Catalyst; 2000–3000 lb}} RCH_2CH_2OH + C_2H_5OH$$

This process is convenient; industrially it is preferable to the sodium reduction because it is cheaper and less hazardous. A number of higher alcohols, which once were rare, are now manufactured in quantity by catalytic reduction.

ESTERS OF INORGANIC OXYGEN ACIDS

The alcohols react with the inorganic oxygen acids, nitrous, nitric, and sulfuric acids, to form esters. The formation of these esters and their hydrolysis are much more rapid than the corresponding reactions with the organic acids.

The esters of nitrous acid are prepared by treating an alcohol and sodium nitrite with sulfuric acid. Ethyl nitrite, C_2H_5ONO, bp 17°, is sold in alcoholic solution as "sweet spirits of nitre." *n*-Butyl nitrite boils at 75°; amyl nitrite at 99°. Both esters serve in the laboratory as sources of nitrous acid which can be used in organic solvents. In the same way methyl nitrate and ethyl nitrate, which are prepared from the alcohols by treatment with a mixture of nitric and sulfuric acids, serve as sources of nitric acid which can be used in organic solvents.

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The volatile esters of nitrous acid find use in medicine. The corresponding esters of nitric acid are powerful, and dangerously sensitive, explosives.

Since sulfuric acid is an acid with two hydrogen atoms, it can form two types of esters just as it can form two classes of salts. **Ethyl sulfuric acid,** $C_2H_5OSO_3H$, is both an ester and an acid. **Ethyl sulfate,** $C_2H_5OSO_2OC_2H_5$, and **methyl sulfate,** $CH_3OSO_2OCH_3$, are examples of neutral esters of sulfuric acid.

Ethyl sulfuric acid (or ethyl hydrogen sulfate) is an oily liquid. It is usually prepared as needed by mixing sulfuric acid and alcohol; the reaction mixture contains water, some unchanged alcohol and sulfuric acid, and the desired ethyl sulfuric acid. Since the substance is both an acid and an ester, it has the characteristic properties of both classes. It forms salts when cautiously treated with bases and is hydrolyzed to alcohol and sulfuric acid when heated with water.

Methyl sulfate is prepared by heating methyl sulfuric acid, CH_3OSO_3H, under *diminished pressure*. The equations for the steps in its preparation are as follows:

$$CH_3OH + H_2SO_4 \rightleftharpoons CH_3OSO_3H + H_2O$$

$$2CH_3OSO_3H \xrightarrow[\textit{in vacuo}]{\text{Distill}} CH_3OSO_2OCH_3 + H_2SO_4$$

Methyl sulfate is a heavy liquid, boiling at 188°, very poisonous, and practically without odor. It is used in place of methyl iodide in certain reactions in which the methyl group is to be introduced into an organic molecule (p. 33). It is much cheaper than the iodide and therefore is quite generally employed for such purposes in industrial processes.

A comparable reaction takes place with ethyl sulfuric acid.

$$2C_2H_5OSO_3H \xrightarrow[\textit{in vacuo}]{\text{Distill}} C_2H_5OSO_2OC_2H_5 + H_2SO_4$$

We have now three different reactions of ethyl sulfuric acid. Which of the three takes place depends upon the experimental conditions: on heating with alcohol to about 130°, ethyl ether is formed (p. 30); on heating alone to above 150°, ethylene is formed (p. 53); and on heating alone *in vacuo* ethyl sulfate is produced.

Halogenation of Acids and Their Derivatives. It will be noticed that in all the reactions previously discussed in this chapter, only the carboxyl group is involved; the alkyl residue has not been modified.

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In halogenation, however, the hydrocarbon portion of the molecule is altered.

The organic acids react with chlorine at elevated temperatures. The reaction is catalyzed by sunlight or by a trace of iodine. Unlike the hydrocarbons (p. 43) the reaction can be controlled and a pure product can be obtained. A hydrogen atom on the carbon next to the carboxyl group (called the *alpha carbon atom*) is replaced. With acetic acid, chloroacetic acid is formed.

$$CH_3COOH + Cl_2 \longrightarrow \underset{\text{Chloro-acetic acid}}{CH_2ClCOOH} + HCl$$

If there is no hydrogen in the alpha position, as in $(CH_3)_3CCOOH$, this reaction obviously cannot occur.

The same reaction occurs much more readily with esters, anhydrides, and acyl chlorides and bromides. A convenient method of brominating the fatty acids which makes use of this fact is known as the *Hell-Volhard-Zelinsky method*. The acid bromide is prepared and brominated in one step. Liquid bromine is dropped onto a mixture of the acid and red phosphorus. The phosphorus tribromide which is first formed reacts with the acid substituting a bromine atom for the hydroxyl group and producing an acid bromide, which is in turn brominated. Finally the reaction mixture is treated with water or alcohol; the acid bromide then reacts in the same way as an acid chloride (p. 88). The reactive bromine atom is substituted by hydroxyl or ethoxyl and the brominated acid or ester obtained is separated and purified by distillation. Even if an excess of bromine is used, the reaction stops after the introduction of one bromine atom in the alpha position. Further bromination requires a high temperature and special conditions. The reactions may be summarized using butyric acid.

$$3Br_2 + 2P \longrightarrow 2PBr_3$$

$$3CH_3CH_2CH_2COOH + PBr_3 \longrightarrow 3CH_3CH_2CH_2COBr + P(OH)_3$$

$$CH_3CH_2CH_2COBr + Br_2 \longrightarrow \underset{\alpha\text{-Bromo acid bromide}}{CH_3CH_2CHBrCOBr} + HBr$$

$$CH_3CH_2CHBrCOBr + H_2O \longrightarrow \underset{\alpha\text{-Bromobutyric acid}}{CH_3CH_2CHBrCOOH} + HBr$$

Since iodine does not react with acids or their derivatives in this manner, the introduction of an iodo atom is accomplished indirectly.

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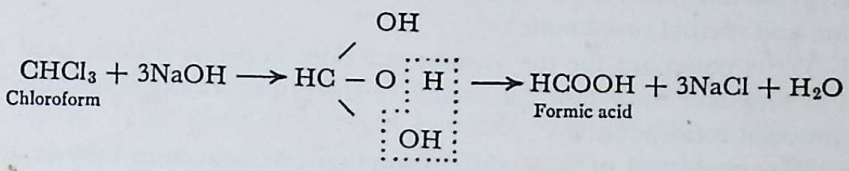
Alpha iodo acids result readily from the following metathetical reaction.

$$RCHBrCOOH + KI \longrightarrow RCHICOOH + KBr$$

Derivatives of Ortho Acids. Compounds of the type $RC(OH)_3$ are unknown, all attempts to prepare them lead to the formation of acids. For example, the hydrolysis of a compound containing three halogen atoms on the same carbon atom yields an acid instead of the expected $RC(OH)_3$.



There is some evidence which indicates that such compounds exist in aqueous solutions of acids or in mixtures of an acid and an equimolecular amount of water, but we cannot be certain of this. It is convenient to have a name for the unknown class, nevertheless, and they are called *ortho acids*. The corresponding alkyl compounds, $RC(OR)_3$, are known and are called *ortho esters*. Thus $HC(OC_2H_5)_3$ is called *ethyl orthoformic ester* (bp 145°). It is prepared by the action of $CHCl_3$ on sodium ethoxide.

$$CHCl_3 + 3NaOC_2H_5 \longrightarrow CH(OC_2H_5)_3 + 3NaCl$$

Ortho esters are rapidly hydrolyzed in the presence of acids with the formation of the corresponding acid and alcohol; thus ethyl orthoformic ester yields formic acid and ethyl alcohol. Ortho esters are surprisingly resistant to the action of alkalies.

QUESTIONS AND PROBLEMS

1. Write complete electronic formulas for the resonating structures of formic acid and the formate ion.

2. What tests would you use to decide whether a certain liquid was an acid, an acid chloride, an acid anhydride, or an alkyl chloride?

3. How would you prepare (*a*) butyric acid and (*b*) *n*-valeric acid from butanol-1?

4. Define and illustrate the following terms: *acyl group*, *alkyl group*, *dissociation constant*, *acid chloride*, *carboxyl group*.

5. In preparing the ester, RCOOR′, from the acid RCOOH and R′OH, why does one add a small amount of a mineral acid and heat the reaction mixture?

6. Write balanced equations for three methods of preparing propionyl chloride from propionic acid. What products would you expect to obtain from the reaction between propionyl chloride and (*a*) ethanol, (*b*) water, and (*c*) ammonia?

7. What is the evidence that in esterification the ester is formed from the acyl group of the acid and the group −OR of the alcohol?

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8. Write balanced equations for the reaction between ethyl butyrate and (*a*) hydrogen, (*b*) water, and (*c*) ammonia.

9. What is the meaning of the term *reversible equilibrium?* What is the effect on such a process of (*a*) raising the temperature, (*b*) adding a catalyst, and (*c*) removing a product?

10. In what types of compounds do hydrogen bonds occur? What is the effect of hydrogen bonding on volatility?

11. What chemical tests could you use to distinguish between ethyl acetate and methyl propionate?

12. Write equations for the various reactions between sulfuric acid and ethyl alcohol and show how the course of these reactions is determined by experimental conditions.

13. How could you prepare alpha bromobutyric acid from butyric acid? How would you prepare the ethyl ester of alpha bromobutyric acid from butyric acid?

14. What is an ortho ester? How are the esters of orthoformic acid prepared?

15. Write structural formulas for: isobutyryl chloride, propionic anhydride, *n*-amyl isobutyrate, and 2-ethylhexanoic acid.

16. What is resonance energy? What effect does resonance have on the distances between atoms in organic compounds?

17. Write the structures of: (*a*) dimethylacetic acid, (*b*) ethyl propionate, (*c*) trimethylacetyl chloride, (*d*) propionic anhydride, (*e*) 3,3-dimethylpentanoic acid, (*f*) *n*-heptyl butyrate, (*g*) potassium formate.

18. Contrast esterification with the process of neutralization.

19 Differentiate by chemical tests between: (*a*) $(CH_3)_2CHOCH(CH_3)_2$ and $CH_3COOCH_2CH_3$, (*b*) CH_3CH_2ONO and $CH_3CH_2COOCH_3$, (*c*) CH_3COONa and CH_3CH_2ONa, (*d*) $HCOONa$ and CH_3CH_2COONa, (*e*) $(CH_3)_2CHCOCl$ and $(CH_3)_3CCl$.

20. Write balanced equations for the reactions: (*a*) acetic acid and thionyl chloride, (*b*) propionyl chloride and ethyl alcohol, (*c*) sodium acetate and *n*-butyryl chloride, (*d*) methyl acetate and sodium hydroxide, (*e*) *n*-amyl alcohol and a mixture of potassium dichromate (excess) and sulfuric acid.

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Chapter 6

GASOLINE AND RUBBER: INDUSTRIAL PRODUCTS FROM PETROLEUM

Fifty years ago the refining of crude petroleum involved very little chemistry. The most important product was kerosene, then widely used in cities, towns, and villages for burning in lamps as a source of illumination. A simple process of distillation was sufficient to produce this material. Today, gasolines with special characteristics are required for modern combustion engines in automobiles and planes. To produce these products certain rather complicated reactions of hydrocarbons are employed. Furthermore, during World War II a large amount of synthetic rubber was produced from petroleum by a series of complex reactions. In addition, other chemical products, such as the alcohols, may be prepared from petroleum. Therefore the whole subject of the industrial use of petroleum and related substances deserves a special chapter, but the chemical transformations involved can only be understood after the basic knowledge presented in the preceding five chapters has been mastered.

In a sense we can treat petroleum, natural gas, and coal together as a source of organic compounds for industrial use. They represent a reservoir of energy which has been stored up in past geologic eras by the reduction of carbon dioxide by living organisms through the use of the sun's energy. (See p. 376.) In the formation of hard coal the reduction has proceeded almost to the point of producing elementary carbon; in petroleum and natural gas it has gone even further to give a mixture of hydrocarbons. Not that the one step precedes the other. At least two types of conversion of vegetable and animal debris were undoubtedly involved in the formation of coal and petroleum.

We can think of the storing of the sun's energy in past geologic ages in terms of the heat evolved when the products we find are burned to carbon dioxide and water. The heat of combustion of pure carbon, as graphite, is 7.8 kg-cal per gram (94 kg-cal per mole); for a liquid hydrocarbon C_nH_{2n+2} the figure is about 11.2 kg-cal per gram (157 kg-cal per CH_2 group, see p. 46); for starch or cellulose the

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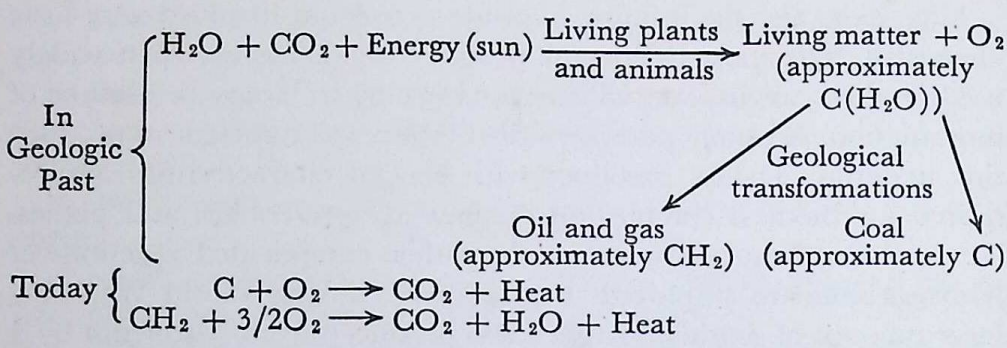
corresponding figure is 4.1 kg-cal per gram, or, since starch and cellulose have the approximate composition $C(H_2O)$, the value per gram of carbon is 30/12 of this or about 10 kg-cal. Restated, these figures mean that the principal storage of energy took place when, through the sun's rays, the plants reduced carbon dioxide to starch or its equivalent (the approximate composition of vegetables and animal material). The subsequent changes which either transformed this to coal or gas involved relatively small changes in the stored up energy.



We shall see that, though the energy stored in these various transformation products of reduced carbon dioxide is nearly the same, their molecular structure is so different that quite different chemical reactions can be brought about through their use.

Coal is used as a solid fuel. On destructive distillation it produces coke and a special class of compounds known as *aromatic compounds* which we shall consider later. From coke by the water-gas reaction (steam at a high temperature) carbon monoxide and hydrogen are cheaply manufactured. In Chap. 8 we shall consider how these materials and coal itself can be converted to liquid fuels and such compounds as the alcohols. In this chapter we shall confine our attention to petroleum and natural gas. In the countries where these materials are found they are the raw materials for liquid fuels.

Natural Gas. Natural gas, which occurs in many parts of the United States and elsewhere, is a mixture composed chiefly of methane, together with ethane and the higher members of the paraffin series of hydrocarbons ($C_4H_{10} - C_8H_{18}$). Even those whose boiling points are above room temperature are present in the form of vapor, just as water vapor is present in ordinary air. Natural gas is usually associated with petroleum, and its origins are probably the same.

A similar gas, composed chiefly of methane, occurs in coal seams.

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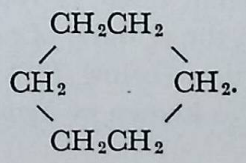
It is worth pointing out that even today we see evidence of the transformation of vegetable material into a hydrocarbon in the evolution of methane from decaying plants and trees under water, and, hence, in the absence of air. The gas is found bubbling up in certain marshy areas and has been known for a long time as *marsh gas*. Its formation may be approximately formulated as follows:

$$\underset{\text{Vegetable material}}{n(CH_2O)} \xrightarrow[\text{Absence of air}]{\text{Bacteria}} n/2CO_2 + n/2CH_4$$

Some of the carbon atoms are oxidized and some are reduced.

Petroleum. Petroleum is found in many parts of the world and each field yields a crude oil with its own characteristics. All crude petroleums are complex mixtures of hydrocarbons and contain in addition small amounts of organic compounds containing nitrogen, sulfur, and oxygen. Many theories as to the origin of petroleum have been suggested but no one theory has been conclusively established. It is generally agreed today, however, that petroleum, like coal, represents the transformation of living material formed in past geologic ages. Perhaps the differences between petroleums simply reflect differences in the plant or animal material transformed in the geologic past. For example, the fats and oils (Chap. 10) are nearer in composition to the hydrocarbons than to the starchy and woody parts of plants. If certain groups of plants or animals (perhaps algae or other unicellular organisms) flourished in past geologic periods and produced large quantities of fats and oils, the subsequent changes of this material might have produced petroleum. On the other hand, the same type of plants which yielded coal under one set of conditions may have produced petroleum under another set of conditions.

In addition to the members of the paraffin series most petroleums contain members of the olefin series and often large amounts of a class of compounds isomeric with the olefins but having a cyclic structure. These latter are called *naphthenic hydrocarbons* or *alicyclic hydrocarbons* and will be discussed later; they have the general formula C_nH_{2n}. The structural formula of one typical representative, cyclohexane, is



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Rings of five and six carbon atoms are commonly present; smaller and larger rings are rare (Chap. 29).

Distillation of Petroleum. Quite apart from the differences in chemical composition and structure, the constituents of petroleum differ enormously in their physical properties. At the one extreme

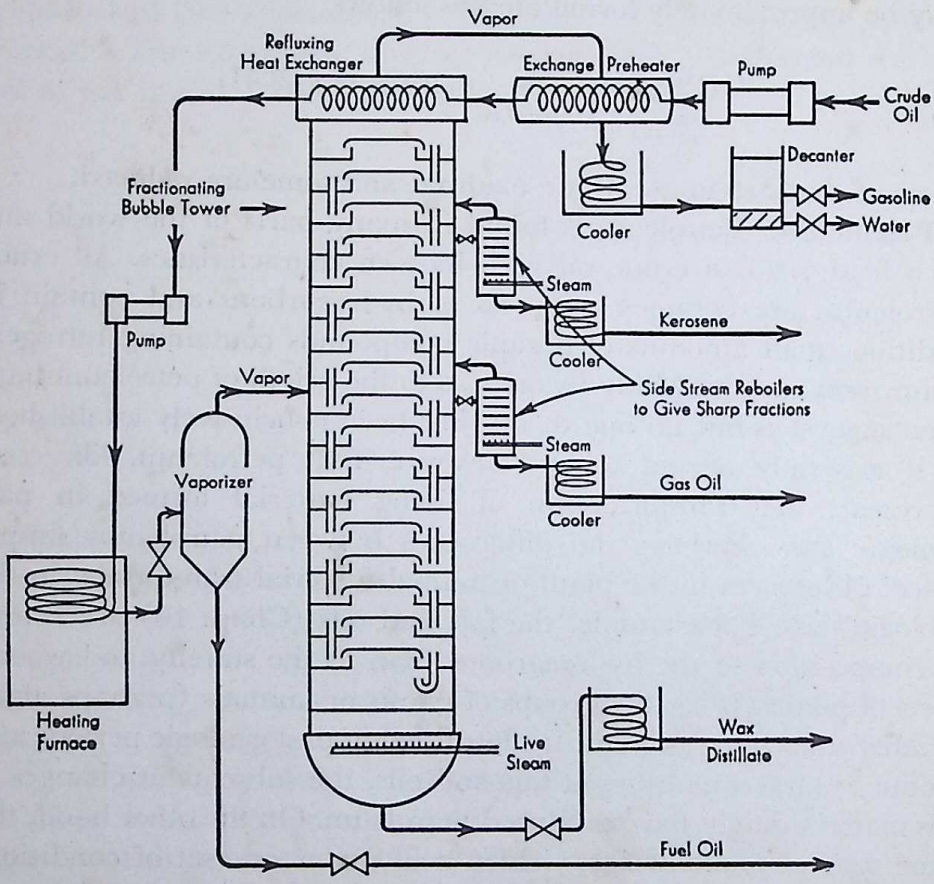

FIG. 5. Diagram of a modern crude oil distillation unit. (It will be noted that the crude oil starts at the upper right hand corner of the diagram and the products are taken off below on the right.)

are the volatile lower members of the paraffin and olefin series; at the other are substances of such high molecular weight that they decompose before they boil (even under reduced pressure). For practical purposes it is necessary to separate the crude oil into different portions corresponding to the different range of volatility of the constituents. Therefore, the first step in the refining of petroleum is distillation.

The lowest boiling portion (below 70°) is sometimes used in the laboratory as a solvent; it is known as *ligroin* or *petroleum ether*. When

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obtained from Pennsylvania oil, it is largely composed of pentanes and hexanes. The material which boils between 85° and 200° is usually sold as **gasoline. Kerosene** is the next fraction; it usually boils in the range 200° to 300°; it will not take fire directly, but, if allowed to moisten a wick in a suitable lamp, it will burn with a pleasant luminous flame.

The residual oil left after the gasoline and kerosene have been distilled is called *topped crude* or *fuel oil*. It is used as fuel. For the most part, fuel oils are blown out from a nozzle in the form of a fine spray mixed with air or steam. This spray is ignited and gives a hot flame. Locomotives and steamships are often fired with crude oil.

Certain kinds of crude petroleum yield on distillation high-boiling oils which are used as **lubricating oils** and a solid, waxlike material, **paraffin,** used in the manufacture of candles. Such oils are said to have a *paraffin base*. From them are also prepared soft greases such as **vaseline,** which is essentially paraffin mixed with some liquid hydrocarbon which has not been removed in the refining. Other varieties of petroleum do not give lubricating oils and paraffin but a thick, black pitch, which is used in roofing and paving; such oils are called *asphaltic*. Pennsylvania petroleum has a paraffin base; Mexican and Californian oils are for the most part asphaltic. "Liquid petrolatum," or "mineral oil," is a carefully refined, high-boiling distillate obtained from certain oils which do not yield paraffin.

Petroleum Refining. The method of further refining petroleum distillates depends on the kind of objectionable components in the fractions. The undesirable materials are certain olefin hydrocarbons (Chap. 4), which cause gum and tar formation, and sulfur compounds which have bad odors and produce sulfur dioxide when burned.

The elimination of the unsaturated hydrocarbons is generally brought about by treating the petroleum fraction for a short time in the cold with fairly concentrated sulfuric acid. Under specially controlled conditions, the paraffins and cycloparaffins are unaffected. To remove traces of acid, the fraction is agitated with sodium hydroxide solution. Sulfur compounds are removed by special methods.

Two other methods of refining are now used. In one the hydrocarbon fraction is extracted with an immiscible solvent which removes the undesirable components. The solvents used are liquid sulfur dioxide, β, β-dichloroethyl ether (p. 202), furfural (p. 602), and phenol (p. 429). The extraction method is widely used in the refining

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of lubricating oils and to a less extent for gasoline refining. The other process of refining is to pass the petroleum vapors through a column of natural clay, silica gel, or activated charcoal. In this method the undesirable components are selectively adsorbed from the petroleum mixture.

THE MANUFACTURE OF GASOLINE

As the demand for a hydrocarbon fuel of high volatility increased with the increase in the number of automobiles, the refining of petroleum changed. Prior to the invention of motor cars, the low-boiling fractions from petroleum distillation were discarded or used to dilute the kerosene. (The temptation in those days was to market a lamp fuel with such a high percentage of volatile constituents as to constitute a fire hazard; there is no such temptation today.) For many years the problem has been to produce enough of the low-boiling fractions. About twenty years ago it was discovered that some of the high-boiling fractions could be partially converted to low-boiling fractions by thermal decomposition at high temperatures. This process, known as *cracking*, soon assumed great importance in the industry. This process then gave way to a second chemical revolution. It was recognized that some types of hydrocarbons performed better in high-compression engines than others. This was followed by the discovery of practical ways of preparing these hydrocarbons. Today, therefore, the manufacture of gasoline involves not only the production of the maximum amount of a low-boiling fraction from petroleum, but the production of a gasoline which will have the maximum content of hydrocarbons of certain structures. To understand this important development we shall have to consider briefly the characteristics of fuels used in automobile and airplane engines.

Octane Ratings of Gasoline. An internal combustion engine which has a high compression ratio is more efficient than an engine with a low one. This has been known for a long time but a limit to the compression was set by the fact that, with the gasolines on the market thirty years ago, excessive knocking occurred if the compression ratio was increased. After a great deal of experimentation it was found in 1922 that such knocking could be largely overcome by adding a small amount of lead tetraethyl (p. 29) to the gasoline. Gasoline thus treated became known as *ethyl gas*.

In the course of the same investigation it was found, by experimentation with samples of pure hydrocarbons, that certain highly branched

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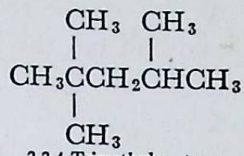
compounds caused less knocking than did others. The octane, 2,2,4-trimethylpentane was arbitrarily chosen as the reference standard and said to have an octane rating of 100; *n*-heptane was given the rating 0, and a scale of octane ratings was thus established. Any gaso-



2,2,4-Trimethylpentane

line could be compared in a suitable test engine with mixtures of these two pure hydrocarbons or samples of gasoline containing varying amounts of lead tetraethyl which had been previously calibrated against the standard mixture.

The straight-chain hydrocarbons $C_4 - C_8$ have very low octane ratings; the corresponding isomeric branched-chain hydrocarbons have octane ratings which are considerably higher. Aromatic hydrocarbons and the cycloparaffins (naphthenes) have high octane ratings, particularly the former. In view of these facts and the complicated mixture of substances present in petroleum it is not surprising that the low-boiling distillates from the refining of petroleum, called *straight-run gasolines*, from different fields differ widely in their octane rating. Tetraethyl lead is added to bring up the octane value, but there is a limit to its effectiveness. Therefore if the hydrocarbons themselves can be converted into branched-chain compounds the octane rating can be raised still more.

The manufacture of "high-octane fuel," so important for the military aircraft of World War II, depended on the preparation of a gasoline rich in branched hydrocarbons. This was done by combining two processes: (1) cracking or thermal decomposition which yields low-boiling saturated and unsaturated hydrocarbons, and (2) the combination of the branched-chain saturated and unsaturated hydrocarbons in the alkylation reaction (p. 62).

Cracking or Thermal Decomposition. This reaction has already been referred to (p. 42). The example given was the decomposition of *n*-butane above 400°.

$$CH_3CH_2CH_2CH_3 \xrightarrow{>400^\circ} \begin{cases} CH_2 = CH_2 + CH_3CH_3 \\ CH_3CH = CH_2 + CH_4 \\ CH_3CH = CHCH_3 + H_2 \end{cases}$$

With higher members of the series the reaction is even more complex.

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Thus from a C_{12} hydrocarbon (bp about 210°) there would be obtained saturated and unsaturated hydrocarbons from C_{11} to C_2 inclusive, together with hydrogen and methane. To the extent that C_4 to C_7 hydrocarbons predominated, the boiling point of the mixture would be brought down to the range required for gasoline. The nature of the products depends on (*a*) the feed stock (i.e., the high-boiling petroleum fraction), (*b*) the temperature and pressure, and (*c*) the catalysts. Some cracking processes operate in the vapor phase, some in the liquid phase (under pressure). When no catalyst is employed the process is referred to as *thermal cracking*.

Alkylation. Cracking under suitable conditions, followed by very careful fractional distillation, enables the gasoline manufacturer (petroleum refiner) to prepare on a large scale such hydrocarbons as ethylene, propylene, butane, isobutane, and the butenes. Isomerization (p. 41) at elevated temperatures and with catalysts further enables him to shift the isomeric butanes one to the other or to the butenes. By the combination of ethylene and isobutane a so-called neohexane (2,2-dimethylbutane) is prepared. This volatile material, which has a high octane rating (94), is an important constituent of the best aviation gasoline.

$$CH_2 = CH_2 + (CH_3)_2CHCH_3 \xrightarrow[100^\circ]{ZrCl_4} \underset{\text{Neohexane}}{CH_3CH_2C(CH_3)_3}$$

Another alkylation reaction of great importance industrially is the combination of isobutane and isobutene to form 2,2,4-trimethylpentane.

$$\begin{matrix} CH_3 \\ \diagdown \\ C \\ \diagup \\ CH_3 \end{matrix} = CH_2 + (CH_3)_2CHCH_3 \xrightarrow[\text{at room temperature}]{H_2SO_4} (CH_3)_3CCH_2CH(CH_3)_2$$

These two examples will suffice to show how, by a combination of "cracking" and "alkylation," the constituents of high-test aviation gasoline can be manufactured.

SYNTHETIC RUBBER

A plentiful supply of gasoline with suitable characteristics is essential to the automobile and airplane industry. So too is a supply of rubber. Indeed the introduction of the automobile and the subsequent enormous increase in the number of motor cars caused a revolution

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in the rubber industry no less than in the petroleum industry. Rubber for tires is an essential for the continuance of a highly industrialized civilization. The United States became painfully aware of this fact when during World War II the supply of rubber was shut off by the capture of the rubber plantations by the Japanese. It was necessary almost over night to build a gigantic synthetic rubber industry to supply rubber for our motorized armies and to keep our civilian economy moving. A study of the creation of this industry involves a knowledge of some very interesting hydrocarbon chemistry. Furthermore, the production of synthetic rubber by one route is closely connected with the production of high-test gasoline. Therefore, it is appropriate to consider this whole subject in a chapter devoted to petroleum products.

Natural Rubber. Before discussing synthetic rubber we must summarize briefly the chemistry of natural rubber. The sap of the rubber tree which grows in certain tropical areas contains a large proportion of a hydrocarbon of high molecular weight. This hydrocarbon is present as an emulsion in the aqueous sap. On heating the sap or adding acetic acid, coagulation occurs. A gummy mass of the hydrocarbon is thus obtained and separated from the water and other constituents of the sap. This material is called *raw rubber* or caoutchouc and is the basic material from which various rubber materials such as automobile tires are manufactured. Before the war large quantities of the sap, or *latex* as it is called, were shipped from the tropics to the rubber manufacturer and the coagulation was brought about as part of the preparation of the finished rubber product. This amounts to using a natural colloidal solution of raw rubber, which for some purposes has advantages.

At the beginning of the twentieth century, rubber assumed a new importance because of the introduction of the automobile. The supply of rubber had to be increased enormously; the production of "wild rubber" from the jungle was totally inadequate and probably could not have been expanded to meet the ever-increasing demand. But a few farsighted men in the 1890's had started the systematic cultivation of rubber trees in Ceylon and the Straits Settlements. (The initial trees were smuggled out of Brazil.) This method of producing crude rubber could be expanded and soon gave a plentiful and cheap source of this raw material so essential for twentieth-century civilization. In the years when the demand was rising sharply (1910–1914) there was much discussion of preparing a synthetic material similar to

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rubber, but the success of the plantations indicated that a synthetic rubber industry would have to produce a very cheap product in order to compete. During World War I, the Germans manufactured a very poor artificial rubber by an expensive process. The importance of rubber to a country's war effort was then relatively slight, so her failure to solve the synthetic rubber problem adequately received very little attention.

Interest in the commercial production of an artificial rubber (so-called synthetic rubber) never completely disappeared, however; and it was recognized that, if a very cheap process could be devised or if a very superior rubber could be manufactured, competition with plantation rubber was a possibility. In the minds of the Germans (after 1933, at least) was the all-important objective of making their nation's economy independent of an outside supply of a vital raw material which could be cut off in time of war.

In the United States an artificial rubber, neoprene, was put on the market for special uses in the late twenties. In Germany, experiments proceeded very far toward the production of a series of artificial rubbers known as the *Bunas*. As the international situation worsened in the 1930's, industrial chemists in every nation became more concerned with the problem of manufacturing a substitute for the raw rubber from the Far East. After Pearl Harbor, the United States was faced with the gigantic task of getting a synthetic rubber industry going before the stock pile of imported raw rubber was exhausted. This was accomplished but with no margin to spare. The processes employed will be described after we have considered the structure of the rubber molecule.

The Structure of the Rubber Molecule. The naturally occurring hydrocarbon which is raw rubber has the formula $(C_5H_8)_x$. The material is insoluble in water, of course, but soluble in many hydrocarbon solvents. The molecular weight is very large and for a long time was the subject of much discussion. (Only in the last twenty-five years have we learned how to study compounds of high molecular weight.) The best estimates, based on osmotic pressure measurements of benzene solutions, now indicate that from 200 to 4000 C_5H_8 units are united in a long chain in the rubber molecule (molecular weight, 13,600 to 272,000), the size of the molecule depending on the previous treatment of the raw rubber. Oxidation of raw rubber with ozone (p. 61) and subsequent hydrolysis of the ozonide show that the double linkages are placed in the chain as indicated below:

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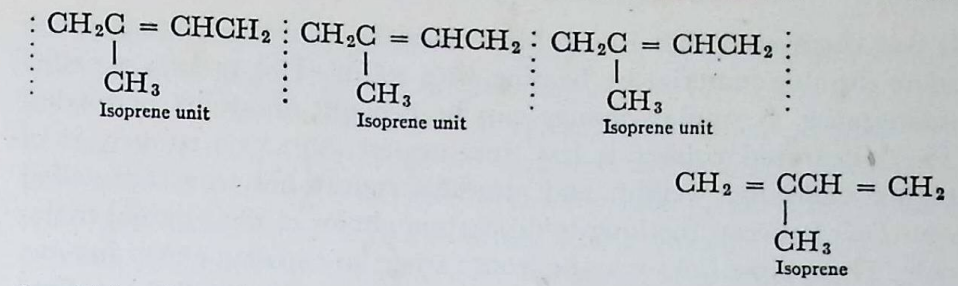
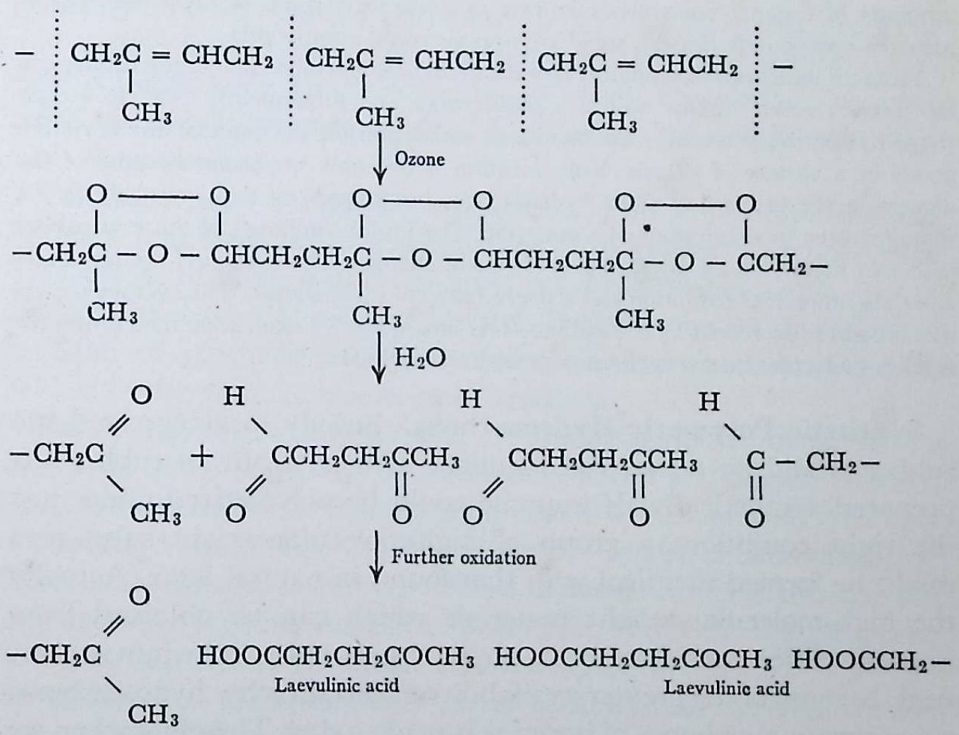


It will be clear that such an arrangement of atoms corresponds to the joining together of a series of isoprene molecules (p. 69) in a regular fashion. It is therefore not surprising that years ago it was discovered that rubber on thermal decomposition yielded isoprene, and that this diolefin on standing with metallic sodium yielded a rubberlike material (which was not identical with rubber).

The evidence for the regularity of the chain in the rubber molecule and the position of the double bonds is given by the 90 per cent yield of the products formed on ozonization.



Vulcanization. Natural rubber without further chemical transformation is not a useful substance. While it is elastic, it is not very tough; it cannot be shaped into useful articles and it deteriorates through slow atmospheric oxidation. More than a hundred years ago

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it was discovered that raw rubber could be converted into a much more durable material by heating with sulfur. This process is called *vulcanization.* A similar change can be brought about by peroxides. The vulcanized rubber is less unsaturated than raw rubber, is of higher molecular weight, and almost certainly has what are called *cross links* between the long hydrocarbon chains of the original molecule. These cross links may be from carbon to carbon or may involve a sulfur atom, or, when peroxides are used, oxygen, or all three. Our knowledge of the molecular structure of vulcanized rubber is far from complete. Indeed in the finished rubber products many varieties of large molecules are probably present.

In the manufacture of tires or similar rubber articles, the raw rubber is milled between warm rollers. This process results in a plastic mass into which sulfur and materials such as zinc oxide and carbon black are then incorporated. The mixture is then heated in a mold to temperatures of 100° to 150°. The vulcanization then takes place. The time of the "cure" is enormously reduced by the introduction of small amounts of organic compounds known as *accelerators;* some of these are organic nitrogen compounds (bases), some are organic sulfur compounds.

From an industrial viewpoint it is of the greatest importance that crude rubber can be "broken down" in the mill to a plastic mass and subsequently "set" to a rigid shape by heating in a mold; this fact alone makes possible the manufacture of rubber goods in a variety of shapes. Vulcanization is not only important because of the change in the properties of the hydrocarbon, but because of the way it allows the manufacturer to manipulate the material. The initial "milling" of the raw rubber probably involves both physical and chemical changes. The oxygen of the air causes a certain amount of oxidation and a degradation of the molecule. The average molecular weight is decreased by the milling. The subsequent vulcanization then unites the smaller molecules into very large ones with "cross linking."

Synthetic Polymeric Hydrocarbons. Strictly speaking, synthetic rubber would be a material identical with natural raw rubber but prepared synthetically. If isoprene could be polymerized under just the right conditions a group of high-molecular-weight substances might be formed identical with that found in natural latex. Actually the high-molecular-weight materials which can be obtained from isoprene differ considerably in physical properties from raw rubber. And, because of the greater availability of certain other hydrocarbons, no commercial polymer of isoprene is made today. Therefore when we speak of synthetic rubber we mean a rubberlike material or rubber substitute.

It was thought at one time that the high degree of unsaturation of

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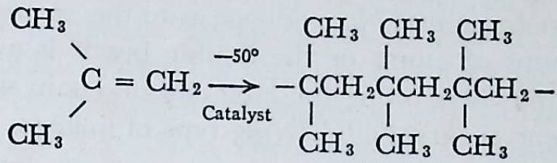
the rubber molecule (one double bond for every five carbon atoms) was the cause of the elasticity of the material. We now know this is not so, for a polymer of isobutene (or isobutylene) called *polyisobutylene* has many of the properties of unvulcanized rubber. This material is prepared by treating isobutene at low temperatures, below $-50°$, with such catalysts as boron fluoride. The molecular weight of the product is 70,000 to 400,000. The substance is a saturated hydrocarbon, yet when properly prepared its physical properties are closely akin to rubber. Therefore unsaturation is not necessary for elasticity.



Polyisobutylene

On the other hand large molecular weight does not by itself confer elasticity on a material for polythene (p. 63) has no elastic properties and neither have many other high-molecular-weight substances we shall consider later. In the present state of our knowledge we cannot correlate the elastic properties of high-molecular-weight substances with their structure.

Polyisobutylene cannot be vulcanized. This fact supplies strong evidence that vulcanization involves the cross linking of carbon chains by decrease of unsaturation. Because polyisobutylene cannot be vulcanized, its industrial uses are limited. It cannot be considered as an artificial or synthetic rubber because it cannot be substituted for rubber in the manufacture of most products.

Butyl Rubber, a Copolymer. It would naturally occur to one that if the polyisobutylene molecule only had a few double bonds in it, a material might be at hand which could be vulcanized. And if so, a material very similar to natural rubber might be manufactured. This turns out to be so and the desired molecule can be synthesized by polymerizing together an olefin, isobutene, and a diolefin, isoprene. The reaction is carried out at a low temperature (below $-50°$) in the presence of aluminum chloride as a catalyst and preferably with ethyl chloride as a diluent; a number of technical engineering difficulties had to be overcome before the process was industrially possible. The material is called *butyl rubber* and is an example of a copolymer. The molecular weight is 50,000 to 250,000.

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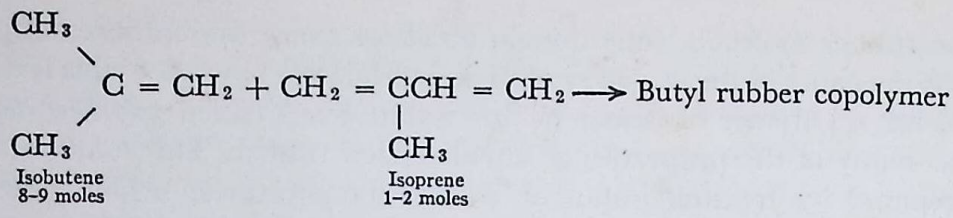
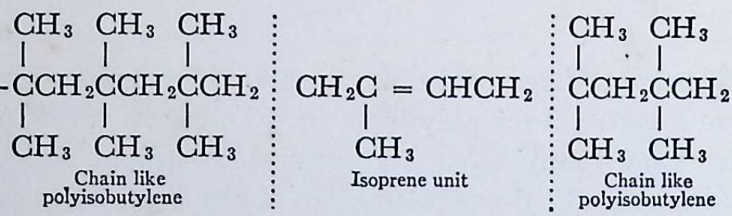


A quantitative study of its reactions with reagents which add to a double carbon bond show that butyl rubber is only about 3 per cent as unsaturated as natural rubber. But this small degree of unsaturation is enough to allow the process of vulcanization to proceed in an essentially normal manner. No evidence as to the arrangement of the constituent groups of atoms or the double bonds is available. Presumably here and there along the long carbon chain similar to that of polyisobutylene occurs the following type of linkage.



This assumes an addition of a molecule of isobutene as $(CH_3)_2C{=}CH|H$ to the 1,4 position of isoprene, a reaction which is very probable. Butyl rubber has certain special properties which make it of value commercially. In particular it is less permeable to gases than are other rubbers. The small quantities of isoprene used in its manufacture can be obtained from the C_5 fraction of certain cracked gasolines or prepared by cracking turpentine (p. 581).

Buna Rubber. The synthetic rubber, so called, produced in the United States during World War II was largely Buna S. This is also a copolymer. It was first developed in Germany. Butadiene is the chief constituent, about 75 per cent by weight; styrene, $C_6H_5CH = CH_2$, is the other. (The grouping C_6H_5 represents a special type of cyclic hydrocarbon structure known as a *phenyl group;* it is derived from the hydrocarbon benzene, C_6H_6, which we shall consider in detail later. As far as synthetic rubber is concerned, this hydrocarbon residue may be considered as analogous to an alkyl group.) In Buna S, unlike butyl rubber, there are almost as many double linkages as in natural rubber. The material can be vulcanized in the usual manner.

The copolymerization of butadiene and styrene is carried out by making an emulsion of these two hydrocarbons in water with the aid of small amounts of soap-

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like substances known as *emulsifying agents*. A catalyst is added which is an oxidizing agent, such as a peroxide, and the whole is heated under pressure to prevent the escape of the volatile butadiene. In this way the equivalent of an artificial latex is formed. The emulsion then passes through a column and is subjected to a sort of "steam distillation" which removes the hydrocarbon which has not polymerized. It is then heated with acid which coagulates the synthetic rubber. This final material is easily separated from the aqueous layer and dried as sheet material in a way very similar to that employed in handling the final product from natural latex.

Neoprene. The synthetic rubbers so far discussed are copolymers. The polymerization of a diolefin by itself would seem to be the most direct route to a material similar to natural rubber. Isoprene is not available in sufficient quantity for a starting material, and the polymers of butadiene by itself have not proved as yet to be as suitable as the copolymers just discussed. There are reports, however, that when polymerized by itself, butadiene yields a satisfactory artificial rubber. No such material has been produced industrially in the United States. The first American synthetic rubber, however, was the result of the polymerization of a diolefin closely related to butadiene and isoprene, namely 2-chlorobutadiene or chloroprene. This material can be manufactured from acetylene by the following reactions.

$$2CH \equiv CH \xrightarrow[\text{copper salt as catalyst}]{\text{Aqueous solution of}} \underbrace{CH \equiv C - CH = CH_2}_{\text{Vinylacetylene}}$$

$$CH \equiv C - CH = CH_2 + \underbrace{HCl}_{\text{Gas}} \longrightarrow \underbrace{CH_2 = CCl - CH = CH_2}_{\text{Chloroprene (bp 60°)}}$$

Chloroprene polymerizes to a rubberlike material more readily than does butadiene or isoprene; the polymerization can be accomplished at room temperature in a short time. The polymerization may be stopped at a stage in which the product has the properties of natural rubber. This material may be mixed with fillers and coloring materials in the same way as natural rubber. The product is then heated for a short time a little above 100° and polymerization occurs further yielding a material having the properties of vulcanized rubber. This rubber is more resistant to the action of solvents and other chemicals than ordinary vulcanized rubber. In spite of its relatively high cost the product has wide industrial use. The structure of the long hydrocarbon chain in chloroprene is probably very similar to that in natural rubber and the last step in the polymerization (the equivalent of vulcanization) may well involve the formation of cross linkages.

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The word *rubber* as applied to such a variety of substances is perhaps unfortunate: We have seen that substances with rubberlike properties are all of high molecular weight, but with a variety of structures. The term *elastomer* has been suggested to include all artificial rubbers and the term *elastoprenes* to cover all the substances in which a diolefin enters as a constituent. Polyisobutylene is designated as an *elastolene*. All elastoprenes can be vulcanized. A rubberlike material with limited industrial use can be prepared by heating ethylene dichloride and sodium polysulfide. Its empirical structure is $(C_4H_8S_4)_x$. It is called *thiokol*. According to the terminology suggested it is a member of the large class of elastomers, but represents a special subdivision known as *elastothiomers*.

ALCOHOLS AND HYDROCARBONS

Alcohols may be prepared from hydrocarbons and hydrocarbons from alcohols by reactions we have already considered. Olefins in the presence of sulfuric acid at room temperature yield alcohols, while alcohols heated with a catalyst yield olefins. When we realize that olefins can be formed by the thermal and catalytic decomposition of paraffin hydrocarbons we realize how interchangeable these materials are from an industrial point of view. This was illustrated in the development of the synthetic rubber industry in the United States during World War II. The manufacture of large quantities of butadiene was the bottleneck of the entire effort. Two basic raw materials were available: starch and petroleum or natural gas. From the former by fermentation ethyl alcohol was prepared (p. 14). This can be converted into butadiene in two catalytic steps involving dehydrogenation, dehydration, and combination.

$$2C_2H_5OH \xrightarrow[\substack{100°\text{–}200° \\ \text{two steps}}]{\text{Catalysts}} CH_2 = CHCH = CH_2 + 2H_2O + H_2$$

Ethyl alcohol, however, can be readily prepared from ethylene, and thus from petroleum by cracking reactions.

$$CH_2 = CH_2 + H_2SO_4 \longrightarrow CH_3CH_2OSO_3H \xrightarrow{H_2O} CH_3CH_2OH$$

During the war the demand for gasoline was so great that it was expedient to use ethyl alcohol from starch as a raw material for butadiene. In this way the supply of low-boiling fractions from "cracked" petroleum (useful for both gasoline and rubber) was supplemented. Under normal conditions, however, ethyl alcohol for commercial purposes can probably be manufactured more cheaply from petroleum and natural gas than by fermentation.

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Higher Alcohols from Petroleum. From the higher olefins, other alcohols can be readily prepared commercially. Isopropyl alcohol is manufactured from propylene, and secondary butyl alcohol from the two normal butenes.

$$CH_2 = CH_2 + H_2SO_4 \longrightarrow CH_3CH_2OSO_3H \xrightarrow{H_2O} CH_3CH_2OH$$

$$CH_3CH = CH_2 + H_2SO_4 \longrightarrow CH_3CH(OSO_3H)CH_3 \xrightarrow{H_2O} CH_3CHOHCH_3$$

$$CH_3CH = CHCH_3 + H_2SO_4 \searrow$$

$$CH_3CH_2CH = CH_2 + H_2SO_4 \nearrow CH_3CH_2CH(OSO_3H)CH_3 \xrightarrow{H_2O} CH_3CH_2CHOHCH_3$$

Tertiary alcohols result from the branched olefins; isobutylene yields tertiary butyl alcohol.

$$\begin{matrix} CH_3 \\ \diagdown \\ C = CH_2 \\ \diagup \\ CH_3 \end{matrix} + H_2SO_4 \longrightarrow \begin{matrix} CH_3 \\ \diagdown \\ C(OSO_3H)CH_3 \\ \diagup \\ CH_3 \end{matrix} \longrightarrow (CH_3)_3COH$$

In all these reactions no attempt is made to isolate the intermdiate alkyl sulfuric acid; the absorption of the gaseous hydrocarbon and the hydrolysis are carried out in one process. The essential parts of the apparatus employed are shown in Fig. 6. The alcohols are obtained by distilling the reaction mixture. By careful control of the conditions in the reaction with sulfuric acid a separation of olefins may be accomplished, since certain olefins react faster than others.

Products from the C_4 Cut. To illustrate the many interrelations of the products from the lower hydrocarbons produced from petroleum, we may consider the "C_4 cut" from the cracking process. This is a mixture of *n*-butane, isobutane, butene-1, butene-2, and isobutene. If butadiene is the product most desired, the mixture can be heated at high temperature with dehydrogenation catalysts; under these conditions *n*-butane yields first the butenes and these in turn yield butadiene.

$$CH_3CH_2CH_2CH_3 \xrightarrow[\text{high temp.}]{\text{Catalysts}} \text{Butenes} \xrightarrow[\text{high temp.}]{\text{Catalysts}} CH_2 = CHCH = CH_2$$

If high-test gas is required, however, the *n*-butane is isomerized by the use of aluminum bromide as a catalyst at 27° and is then combined in the alkylation reaction with the isobutene present; if there is an insufficient quantity of isobutene, catalytic dehydrogenation of a fraction of the isobutane is employed. For polyisobutylene, butyl rubber, or tertiary butyl alcohol all the isobutane is dehydrogenated. The butenes

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can be hydrogenated to *n*-butane and isomerized to isobutane which is dehydrogenated to isobutene, or they may be isomerized to the branched-chain hydrocarbons directly by catalysts at 300° to 350°. (The isomerization does not go to completion.)

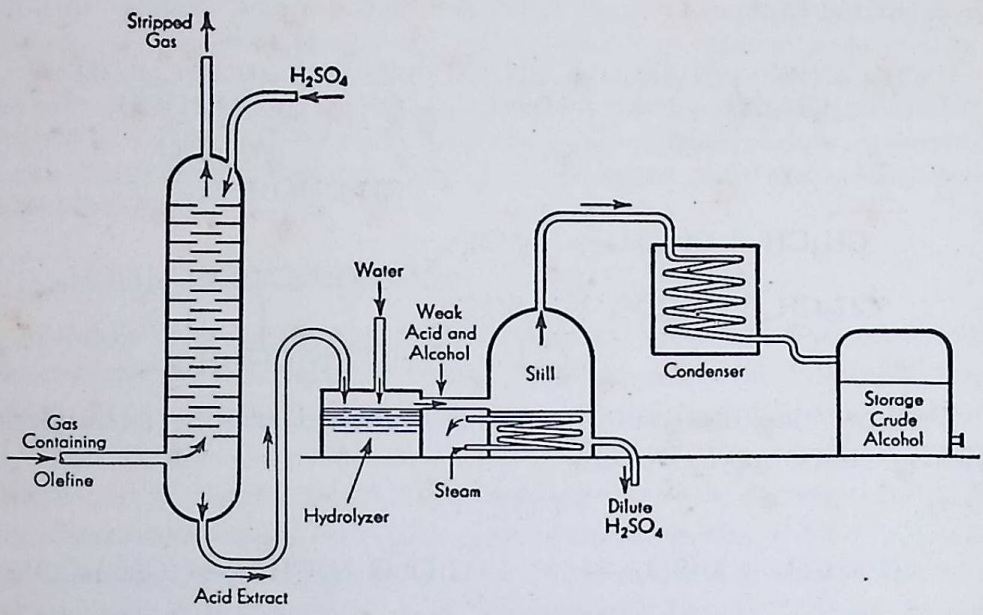
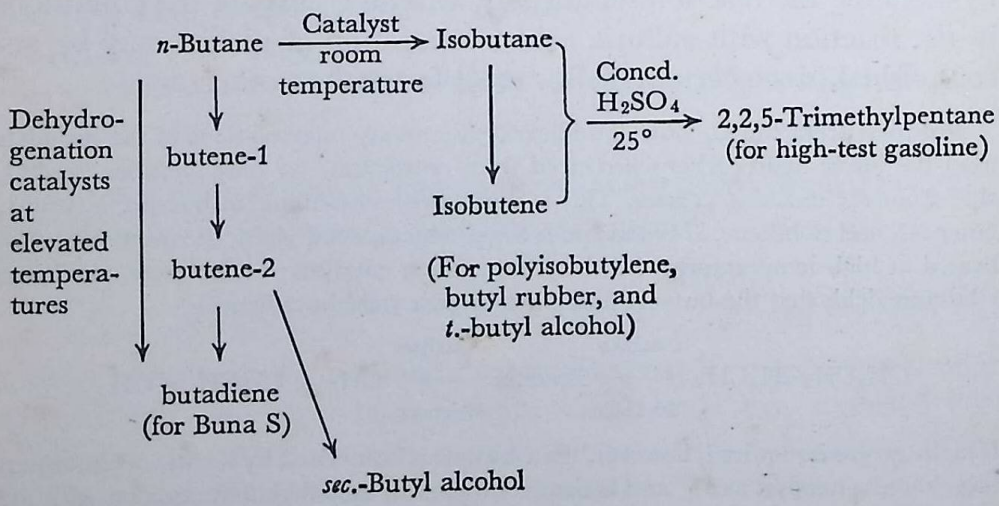


FIG. 6. The essential parts of the apparatus used in the preparation of alcohols from unsaturated hydrocarbons.

It may be noted that if the straight-chain compounds were the more valuable, isomerization of isobutane to butane at 500° could be employed and the isobutene transformed by the same route after hydrogenation to isobutane.



Equilibria and Energy Relations. The industrial manipulation of the C_4 hydrocarbons summarized above is one of the best

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examples of changing the equilibrium constant and hence the course of the reaction by changing the temperature over a wide range. At a given temperature the value of the equilibrium constant is related to the amount of heat evolved in the reaction, but unfortunately the relation is not a simple one. It involves a knowledge of the heat which would be absorbed in bringing each reactant and product from the absolute zero to the reaction temperature. This can be calculated if one knows for each reactant and product the specific heat (heat capacity) from the absolute zero to the reaction temperature, and the heat absorbed in fusion and vaporization. These thermal data are available in a few instances and can be estimated with some accuracy in others. The heat evolved follows from a knowledge of the heats of combustion (p. 45). Therefore the equilibrium constant can be calculated approximately for most organic reactions and at various temperatures. Such calculations show what is possible *provided the desired reaction can be made to proceed rapidly enough by means of a suitable catalyst.* Such calculations have been of great importance in developing the industrial chemistry of the lower paraffins and olefins. The following rough generalizations summarize the pertinent facts.

1. *Isomerization.* The same number of molecules are present on both sides of the equation; therefore, equilibrium is not affected by pressure. The reaction, normal isomer to branched isomer, is exothermic; the normal isomer is favored at higher temperature. The heat evolved is not great; therefore the shift in the ratio $\frac{\text{isobutane}}{n\text{-butane}}$ is only from 4.0 to 0.5 as the temperature rises from 25° to 625°.

2. *Hydrogenation and Dehydrogenation.* There are two molecules on one side, one on the other; therefore, hydrogenation is favored by pressure. At room temperature, hydrogenation is strongly exothermic; therefore, the equilibrium is enormously in favor of the hydrogenated product. An increase in temperature shifts the equilibrium in favor of the unsaturated product *rapidly*, because the heat evolved is large. At 1 atm the ratio of $\frac{\text{propane}}{\text{propylene}}$ in equilibrium with hydrogen shifts from about 10^{15} at 25° to approximately unity at about 700°. A similar situation is met in the relation between butene-2 and butadiene.

3. *Alkylation and Dealkylation.* The formal reaction is similar to hydrogenation and dehydrogenation, with the simple hydrocarbon taking the place of hydrogen; for example, $CH_4 + CH_2 = CH_2 \longrightarrow CH_3CH_2CH_3$. No general catalyst for the addition at low temperature has been found and only alkylation reactions with branched saturated hydrocarbons have as yet been realized. It is important to remember that this is a question of rates. Pressure favors the alkylation. The energy relations are similar to hydrogenation. The alkylation reaction is strongly exothermic at room temperature, and the equilibrium shifts rapidly in favor of the decomposition products as the temperature rises. Calculations show that at 25° the equilibrium constant

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$K = \frac{(\text{propane})}{(\text{ethylene})(\text{methane})}$ = about 10^7, while at 300°, the value is 1, and at 700 it is 0.05. This means immeasurably small amounts of ethylene and methane would be in equilibrium with propane at room temperature, but ethylene and methane predominate at 700°.

4. *Hydration and Dehydration.* Again, formally, this reaction is similar to hydrogenation and dehydrogenation with water replacing hydrogen. The mode of addition is determined by Markownikoff's rule.

At room temperature the addition of water is exothermic, but not so strongly as hydrogenation or alkylation and the reaction is more nearly balanced; the heat evolved at 25° is about 10 kg-cal for ethylene, product and factors being in the gaseous state. In the vapor phase (reactants and product gases) above 100° the equilibrium is in favor of the unsaturated hydrocarbon at 1 atm pressure.

Le Chatelier's Principle. While equilibrium constants cannot be calculated from a knowledge of the heat of reaction alone (specific heat data are also required), the shift of the constant can be so calculated. In a qualitative way the direction and magnitude of the shift can be predicted by the application of Le Chatelier's principle, which is therefore a convenient guide to a first approximation in this field. A consideration of the quantitative relation between the change of the equilibrium constant and heat of the reaction would take us too far into physical chemistry.

Le Chatelier's principle states that when a system at equilibrium is disturbed the system will shift in such a way as to minimize the effect of the disturbance. In applying this principle in organic chemistry we must conjure up before our minds the imaginary state of the balanced reaction for, as we have seen, actual equilibria in organic reactions are the exception rather than the rule. But, if we imagine that a suitable catalyst has been found and that no side reactions are occurring, we can always suppose the reaction to be in equilibrium as it is in esterification and hydrolysis. First, think of applying pressure. If the same numbers of molecules are involved in both forward and back reactions, the process proceeds without significant change in volume, and pressure therefore will not affect the equilibrium. But, if the reaction proceeds with a decrease in volume (as in 2, 3, and 4 above), the effect of the applied pressure can be offset by the reaction proceeding from left to right.

$$A + B \longrightarrow AB$$

The decrease in volume offsets the disturbance of pressure applied to the equilibrium mixture of A, B, and AB.

Similarly with a change in temperature. If the temperature of the imaginary equilibrium mixture is raised a few degrees, the mixture can cool itself by shifting in the direction of *absorbing heat.* Therefore, it is evident that endothermic reactions are favored when the temperature is raised.

Since an exothermic reaction such as hydrogenation when written in the opposite sense, as a dehydrogenation reaction, is endothermic, this principle applies to all reactions where heat is absorbed or evolved. Where there is little or no heat absorbed or evolved, as in esterification, the equilibrium is not influenced by change in temperature (p. 96). It is convenient to remember that a balanced endothermic reaction proceeds further the higher the temperature.

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QUESTIONS AND PROBLEMS

1. Outline the steps in the distillation of petroleum and the refining of the petroleum distillates.

2. What is the meaning of the "octane number" of a gasoline?

3. Define and illustrate the following terms: *copolymer*, *elastomer*, *latex*, *accelerator*, *raw rubber*.

4. Explain the different ways in which plants and animals stored solar energy. At what stage in the process did the principal storage of energy take place?

5. What relationships can you point out between the structure of hydrocarbons and their octane value?

6. Show how the alkylation of olefins with paraffins serves as a method of synthesizing paraffin hydrocarbons. Explain, in terms of your answer to Question 5, why alkylation is so valuable in the manufacture of high-test gasoline.

7. What is the structure of the natural rubber molecule?

8. What is the difference in structure between polyisobutylene and butyl rubber? How does this difference account for the ability of polyisobutylene to undergo polymerization?

9. Outline the process for the manufacture of Buna S.

10. Show how butadiene can be prepared from coal, from petroleum, and from starch.

11. Describe the preparation of the alcohols from petroleum.

12. What are thiokol and neoprene? How are they prepared?

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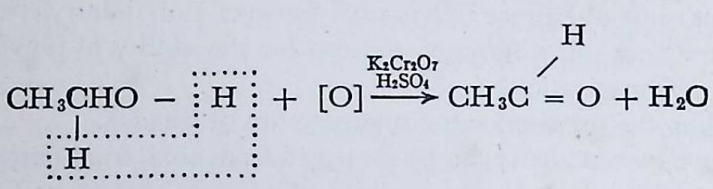
Chapter 7

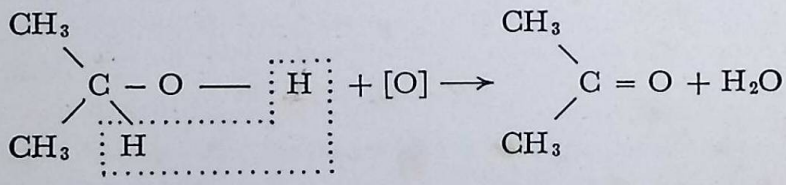
ALDEHYDES AND KETONES

Oxidation of Primary Alcohols. When a primary alcohol is cautiously oxidized, it is possible to isolate a substance intermediate between the alcohol and the corresponding acid. Such a compound is known as an *aldehyde*. For example, if ethyl alcohol is slowly added to a mixture of sodium dichromate and sulfuric acid, and the volatile products allowed to distill, we find in the distillate considerable quantities of **acetaldehyde,** CH_3CHO.



If, however, we arrange the apparatus with a reflux condenser so that the volatile aldehyde is returned to the oxidizing agent, the product is acetic acid, because the aldehyde is further oxidized to the acid.

Oxidation of Secondary Alcohols. When a secondary alcohol is oxidized, a ketone is formed.



Here there is little danger that the oxidation will proceed too far; ketones are oxidized only with difficulty and never to a product with the same number of carbon atoms.

It will be noted that both these processes of oxidation consist in the removal of two hydrogen atoms which have been indicated by heavy print in the formulas. The process is really one of **dehydrogenation;** this term is often applied to it. We may suppose that the function of the oxidizing agent is to supply oxygen to combine with the two hydrogen atoms and form water.

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In the presence of metallic copper at 300°, primary and secondary alcohols spontaneously lose hydrogen and form aldehydes or ketones and gaseous hydrogen.

$$RCH_2OH \xrightarrow[300^\circ]{\text{Copper}} RCHO + H_2$$

$$R_2CHOH \xrightarrow[300^\circ]{\text{Copper}} R_2CO + H_2$$

This provides a convenient method of preparing ketones and aldehydes from the corresponding alcohols. Copper chromite (p. 98) is also used as a catalyst for this dehydrogenation and often leads to better yields.

Behavior of Tertiary Alcohols with Oxidizing Agents. An examination of the structure of a tertiary alcohol would lead one to predict that an oxidation process similar to that of primary and secondary alcohols would be impossible for there is no hydrogen atom attached to the C—OH group. Tertiary alcohols are, indeed, oxidized with difficulty, and are broken into smaller molecules by the reaction. We may thus say that *only primary and secondary alcohols can be oxidized to compounds containing the same number of carbon atoms as the original alcohol.* Since aldehydes, but not ketones, can be further oxidized, it is evident also that *only primary alcohols can be oxidized to an acid with the same number of carbon atoms.*

Distinction between Primary, Secondary, and Tertiary Alcohols. This difference in the behavior of primary, secondary, and tertiary alcohols on oxidation enables us to distinguish between them. The student should convince himself that this is a necessary consequence of the structural theory by writing the formulas of the isomeric alcohols and the equations for the reactions.

ALDEHYDES AND KETONES

The Carbonyl Group. Aldehydes and ketones both contain the group $>C=O$; this is known as the *carbonyl* group. Since they both contain this reactive group, they have many chemical properties in common. The differences between aldehydes and ketones are due to the fact that in the aldehydes, $\begin{matrix} H \\ R \end{matrix}\!\!>C=O$, we have one alkyl group and

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one hydrogen atom attached to the carbonyl group, and in ketones, $\begin{matrix} R \\ R \end{matrix}\!\!>C=O$, two alkyl groups.

It is customary to write the formula of an aldehyde, $\begin{matrix} H \\ R \end{matrix}\!\!>C=O$, as RCHO. Formulas corresponding to RCOH are never used as this might signify that the hydrogen was attached to oxygen.

Physical Properties of Aldehydes. The physical properties of the lower members of the homologous series of aldehydes are given below. The first five all have a peculiar sharp odor.

PHYSICAL PROPERTIES OF THE SIMPLER ALDEHYDES

Name	*Formula*	*Boiling Point*	*Solubility Grams per 100 Grams of Water*
Formaldehyde	HCHO	− 21°	Miscible
Acetaldehyde	CH_3CHO	+ 20°	Miscible
Propionaldehyde	CH_3CH_2CHO	+ 50°	20
n-Butyraldehyde	$CH_3CH_2CH_2CHO$	+ 76°	3.6
Isobutyraldehyde	$(CH_3)_2CHCHO$	+ 61°	11
n-Valeraldehyde	$CH_3(CH_2)_3CHO$	+103°	
n-Capronaldehyde	$CH_3(CH_2)_4CHO$	+128°	
n-Heptaldehyde	$CH_3(CH_2)_5CHO$	+155°	

The higher aldehydes have a pleasant odor. Some of them occur in fruits and plants; for example, nonyl aldehyde, $C_8H_{17}CHO$, is found in geranium oil.

Nomenclature of Aldehydes and Ketones. The aldehydes are named from the acids to which they may be oxidized, as is illustrated by the names in the table above. They are also named by the Geneva system, the suffix *-al* being employed. Thus, $CH_3(CH_2)_3CHO$ is pentanal and $(CH_3)_2CHCH_2CHO$, 3-methylbutanal.

The ketones may be classified as simple ketones, RCOR, in which the alkyl groups are the same, and mixed ketones in which they are different, RCOR′. One method of naming ketones is illustrated in the following table. By the Geneva system, the longest chain of carbon atoms is named and the suffix *-one* added, followed by a number which indicates the position of the carbonyl group. Thus, $CH_3COCH_2CH_3$ is butanone-2; $(CH_3)_2CHCOCH_2CH_3$, 2-methyl-pentanone-3.

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KETONES

Name	*Formula*	*Boiling Point*	*Solubility Grams per 100 Grams of Water*
Acetone	CH_3COCH_3	56°	Miscible
Methyl ethyl ketone	$CH_3COCH_2CH_3$	80°	25
Diethyl ketone	$CH_3CH_2COCH_2CH_3$	102°	About 20
Methyl *n*-propyl ketone	$CH_3COCH_2CH_2CH_3$	102°	4
Methyl isopropyl ketone	$CH_3COCH(CH_3)_2$	93°	—
Ethyl *n*-propyl ketone	$CH_3CH_2COCH_2CH_2CH_3$	124°	Very slightly soluble
Ethyl isopropyl ketone	$CH_3CH_2COCH(CH_3)_2$	115°	
Methyl *n*-butyl ketone	$CH_3COCH_2CH_2CH_2CH_3$	127°	
Methyl isobutyl ketone	$CH_3COCH_2CH(CH_3)_2$	119°	
Methyl *t*.-butyl ketone	$CH_3COC(CH_3)_3$	106°	

Preparation of Ketones. Aldehydes and ketones are often prepared from the *corresponding alcohols* by oxidation or dehydrogenation, as explained in the first paragraphs of this chapter (p. 124).

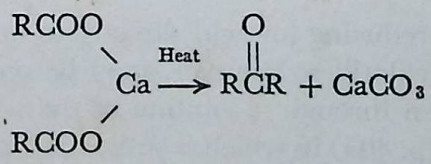
1. From Acids. We may also prepare ketones from the *corresponding acids*.

The vapor of the acid is passed through a hot tube containing manganese oxide, MnO, or thorium oxide, ThO_2, as a catalyst. On the surface of the catalyst a reaction takes place yielding the ketone.

$$2RCOOH\ (\text{vapor}) \xrightarrow[300^\circ]{MnO} R_2CO + H_2O + CO_2$$

Mixed ketones, for example, methyl ethyl ketone, may be prepared by passing a mixture of the two acids in question over the catalyst. In addition to the mixed ketone, a mixture of the other two possible ketones is always formed. For this reason it is preferable to prepare such mixed ketones by oxidizing the corresponding secondary alcohol, if it can be readily procured.

An older and less satisfactory method of preparing ketones, of which the catalytic process just described was a development, involved heating the calcium salt of an acid to a high temperature.



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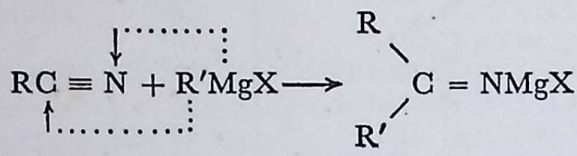
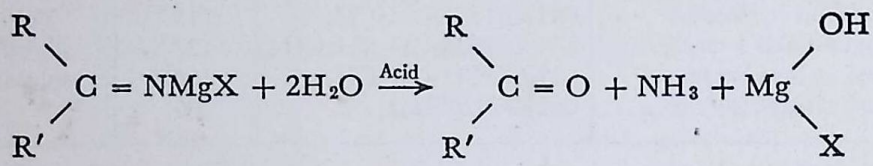
2. From Nitriles. The action of a Grignard reagent on a nitrile yields a magnesium compound which is easily hydrolyzed on treatment with acid forming a ketone and ammonia. The general equations are given below, the symbol R′ being used to indicate that the resulting ketone may be either symmetrical or unsymmetrical.





3. From Dihalides. The hydrolysis of a compound having two halogen atoms on the same carbon atom might be expected to produce a substance having the group $C(OH)_2$. Actually either an aldehyde or ketone is formed. All but a few compounds (see chloral, p. 145) containing two hydroxyl groups on the same carbon atom are unstable, and lose water forming a carbonyl group.

$$CH_3CCl_2CH_3 + H_2O \xrightarrow[\text{catalyst, } 100^\circ]{\text{Alkaline}} CH_3COCH_3 + 2HCl$$

Preparation of Aldehydes. Similar procedures may be used for the production of aldehydes. By passing the vapors of an acid and formic acid over a suitable catalyst, considerable aldehyde is formed.

$$RCOOH + HCOOH \xrightarrow[300^\circ]{MnO} RCHO + H_2O + CO_2$$

The destructive distillation of a mixture of the calcium salt of an acid and calcium formate yields some aldehyde together with the corresponding ketone.

$$(RCOO)_2Ca + (HCOO)_2Ca \longrightarrow 2RCHO + 2CaCO_3$$

$$(RCOO)_2Ca \longrightarrow RCOR + CaCO_3$$

The problem of reducing an acid directly to an aldehyde has not been solved. Acid chlorides, however, may be reduced catalytically by passing hydrogen through a solution of the acid chloride in dry benzene or xylene (p. 403) in which is suspended a palladium catalyst

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on barium sulfate. The reaction is generally carried out at the boiling point of the solvent.

$$RCOCl + H_2 \xrightarrow{\text{Catalyst}} RCHO + HCl$$

Oxidation of Aldehydes. The chief difference between aldehydes and ketones is that the former are very easily oxidized to an acid while the latter are oxidized only with difficulty. Furthermore, when ketones are oxidized, a carbon-carbon bond is broken, and acids with fewer carbon atoms are the products. The difference in the ease of oxidation is the basis for several tests which enable us to distinguish between the two classes of substances. When aldehydes are warmed with an **ammoniacal solution of silver nitrate,** they precipitate metallic silver which often comes down in the form of a beautiful mirror. The aldehyde is oxidized to the corresponding acid which is present in the alkaline solution as the ammonium salt.

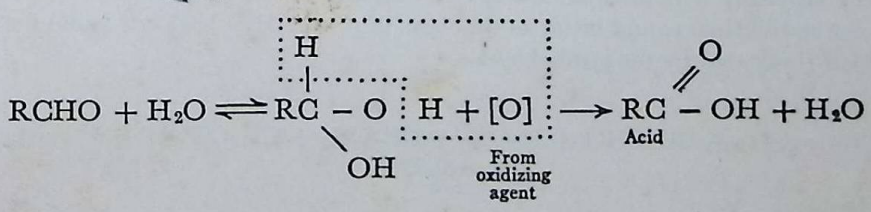
$$RCHO + 2AgOH + NH_4OH \longrightarrow RCOONH_4 + 2Ag + 2H_2O$$

Similarly, when an alkaline solution of copper hydroxide containing sodium tartrate (essentially copper hydroxide in solution) — **Fehling's solution** — is warmed with an aldehyde, red cuprous oxide is precipitated.

$$RCHO + 2Cu(OH)_2 + NaOH \longrightarrow RCOONa + Cu_2O + 3H_2O$$

These tests are very easy to carry out and are frequently employed. Ammoniacal silver nitrate and Fehling's solution are often spoken of as *mild* oxidizing agents, since most organic compounds are not attacked by them.

Mechanism of the Oxidation. The oxidation of aldehydes in solution is another example of dehydrogenation. There is considerable evidence to indicate that the aldehydes are hydrated in water solution; these hydrates, like the primary and secondary alcohols, contain the group $>C<^{H}_{OH}$. The following equation represents the course of the oxidation of aldehydes.



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Energy Relations in the Oxidation of Aldehydes. From the heats of combustion we can calculate that the heat evolved in the reduction of acetic acid vapor to acetaldehyde and water would be very small. Accurate calculations involving specific heats show that, conforming to our general rule, the equilibrium constant of the *hypothetical reaction*, acetic acid + hydrogen to give acetaldehyde + water, would correspond to an appreciable quantity of reactants and products at room temperature or slightly higher. Actually no catalyst has been found which will make this hypothetical balanced reaction proceed in either direction in the vapor state or in solution. Nor has it been possible even to find a catalyst by which acetic acid as a gas, or a liquid, or in solution as a salt can be reduced to ethyl alcohol, though here the equilibrium would be in favor of the hydrogenation product at room temperature and atmospheric pressure. Referring to the mechanism of the oxidation of aldehydes as proceeding through a hydrate, we find from accurate calculations that the equilibrium should favor hydrogen and acetate ion at those acidities where practically all the acetic acid is present as the ion.

Hypothetical reaction:

$$CH_3CHO + H_2O \underset{\text{Rapid balanced reaction}}{\rightleftharpoons} CH_3CH\begin{matrix}/OH\\ \backslash OH\end{matrix} + OH' \rightleftharpoons CH_3COO^- + H_2O + H_2(g)$$

At 25°, the equilibrium is theoretically somewhat in favor of the right-hand side, but no catalyst is known which will bring about the reaction in either direction.

The reason why no satisfactory catalyst has been found for the formation of gaseous hydrogen and an acid anion from an aldehyde, water, and a hydroxyl ion probably resides in the fact that the aldehyde itself is either readily reduced to an alcohol or undergoes an aldol condensation (p. 137). The first leads to the Cannizzaro reaction (p. 149), the second to complex condensation products.

Although free hydrogen is not evolved by the use of any known catalyst on an alkaline solution of acetaldehyde (nor can the reverse reaction be made to go under pressure), the fact that this reaction is so nearly balanced has very important consequences. The hydrogen atoms of the aldehyde hydrate can be used in a variety of reduction processes. That is why we speak of an aldehyde as a reducing agent, but do not usually speak of an alcohol as a reducing agent though the hydrogen atoms of an alcohol can also be removed by an oxidizing agent. We must distinguish clearly in considering oxidation and reduction reactions (dehydrogenation and hydrogenation) between rates and equilibria, the latter of which are determined by energy considerations. If we write a hypothetical reaction in which two hydrogen atoms are shifted from one molecule to another, we can calculate the equilibrium from heats of combustion and specific heat data. But the reaction may not be realizable because we cannot find a suitable catalyst. For example:

The following hypothetical reaction corresponds to a very large heat evolution and the equilibrium would be far to the right, but no catalyst has been found for the reaction (indicated by the symbol $\not\rightarrow$).

$$CH_2 = CH_2 + CH_3CHO + H_2O \underset{\text{No catalyst known}}{\overset{25°}{\not\rightarrow}} CH_3CH_3 + CH_3COOH + 37 \text{ kg-cal}$$

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On the other hand it has been possible to find a catalyst which at 250° to 300° will shift hydrogen from an alcohol to an ethylenic hydrocarbon. Thus the following reaction takes place in the presence of copper chromite containing zinc, nickel and barium

$$CH_2 = CH_2 + CH_3CHOHCH_3 \xrightarrow[250°-300°]{\text{Catalyst}} CH_3CH_3 + CH_3COCH_3 + 20 \text{ kg-cal}$$

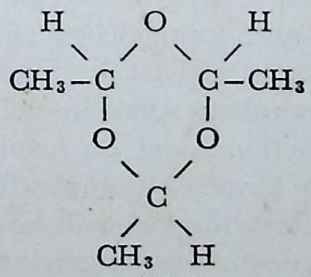
We could list a number of unsaturated substances already encountered, such as hydrocarbons, aldehydes, ketones, and acids, in accordance with their theoretical ability to remove hydrogen from the corresponding hydrogenated compounds; e.g., ethylenic hydrocarbons should take hydrogen away from alcohols in the presence of a suitable catalyst. But, since the catalysts are so important and for many of the reactions are unknown, such a list might be very misleading.

Inorganic reagents which can use up hydrogen, such as potassium dichromate, potassium permanganate, silver oxide (or its equivalent, ammoniacal silver nitrate), cupric oxide (or its equivalent in Fehling's solution) can likewise be listed in terms of their power to oxidize or reduce one another; but again such a list is often misleading in organic chemistry because it does not tell whether a reaction between one of these reagents and an organic compound will proceed at an appreciable rate.

Polymerization of Aldehydes. Aldehydes and ketones differ in still another respect. When an aldehyde is treated with a small amount of mineral acid, it is almost completely *polymerized* (p. 63). The polymer is a substance which has a molecular weight three times that of the aldehyde.

$$3RCHO \overset{\text{Catalyst}}{\rightleftharpoons} (RCHO)_3$$

The reaction is reversible in the presence of acid. The polymer of acetaldehyde is known as *paraldehyde*. It is a much higher boiling liquid than acetaldehyde and, unlike acetaldehyde, is insoluble in water. It has none of the characteristic reactions of the aldehydes; for example, it will not reduce Fehling's solution. In the polymer the three aldehyde molecules are joined together in a ring containing alternate carbon and oxygen atoms. Paraldehyde is used as a hypnotic.



Paraldehyde

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At low temperatures acetaldehyde is polymerized by dilute sulfuric acid to a crystalline solid known as *metaldehyde*. Like paraldehyde it shows no aldehydic properties. It can be converted into acetaldehyde by distilling with dilute acid. It burns in air with a nonluminous flame and is marketed as a solid fuel for household use in place of "solid alcohol." The trade name for it is "Meta." Metaldehyde is a tetramer, $(CH_3CHO)_4$.

Importance of the Catalyst. A consideration of the reversible polymerization of an aldehyde is of interest. The equilibrium with most aldehydes is in favor of the polymer, but measurable quantities of both factors and product are present. That is, when pure acetaldehyde is treated with a few drops of sulfuric acid, it rapidly polymerizes until more than 95 per cent of the material is present as paraldehyde; the process then reaches equilibrium. In the same way, when pure paraldehyde is treated with a little acid, a few per cent depolymerizes, but no more. We are here dealing with a state of dynamic equilibrium, just as in esterification. And, as in esterification, the heat evolved in the reaction being small we would expect (1) a nearly balanced equilibrium, and (2) only slight shift of the equilibrium constant with temperature.

It must be clearly borne in mind that the reaction is reversible *only* in the presence of a suitable catalyst, such as a mineral acid. Pure acetaldehyde or pure paraldehyde may be kept unchanged for a long period of time and may be distilled without decomposition. The rate of the reaction in either direction becomes appreciable only in the presence of a catalyst. For example, to prepare paraldehyde we treat cold acetaldehyde with a few drops of acid, and, after a few minutes, when equilibrium has been established, wash away with water or dilute alkali both the unchanged aldehyde and the catalyst. The paraldehyde can then be dried, distilled, and kept just like any other organic substance.

To convert paraldehyde (bp 124°) into acetaldehyde it is only necessary to add a few drops of mineral acid and slowly distill. Since the acetaldehyde boils at 20°, it rapidly volatilizes and is thus removed from the equilibrium mixture. More paraldehyde then depolymerizes, and this process continues until all the paraldehyde has depolymerized and distilled over in the form of acetaldehyde. This is an excellent example of the completion of a reversible reaction by removing one of the products from an equilibrium mixture which contains appreciable quantities of factors and products.

Polymers of Formaldehyde. Trioxane, $(HCHO)_3$, is the cyclic trimer from formaldehyde which corresponds in structure to paraldehyde. It is a crystalline solid which has no aldehyde properties, but which decomposes on heating to form gaseous formaldehyde.

In addition to trioxane, formaldehyde forms solid polymers of unknown molecular weight, $(HCHO)_x$. These are known as *polyoxymethylenes*. They are amorphous solids insoluble in all solvents; they show no aldehydic reactions, and on heating decompose to give formaldehyde. They are formed by evaporating an aqueous solution of the aldehyde and on treating an alcoholic solution with acid. The large molecule present in these polymers is composed of a chain of

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40 to 100 formaldehyde units. A portion of this chain may be represented thus:

$$\cdots OCH_2-O-CH_2-O-CH_2-O-CH_2-O-CH_2-O-CH_2\cdots$$

Depending on the method of formation, the terminal groups of the long chain are either $-OH$ or $-OCH_3$ (the latter from the methyl alcohol used in the preparation). Acetaldehyde and the higher homologs of formaldehyde do not form such long-chain polymers under usual conditions. However, by subjecting the liquid aldehyde to very high pressure (5000 to 10,000 atm) for some hours, such high-molecular polymers are formed from the higher aldehydes. They resemble paraformaldehyde in their physical properties, but slowly revert to the liquid aldehyde when kept at atmospheric pressure.

ADDITION REACTIONS OF THE CARBONYL GROUP

So far, we have stressed the differences between aldehydes and ketones. We shall now consider their many similarities. The carbonyl group, $>C=O$, in both substances is very reactive and adds many reagents. Such addition reactions, as we have seen, are characteristic of substances with a double linkage (p. 56). The double linkage in aldehydes and ketones is between carbon and oxygen in contrast with that in ethylene which involves only carbon atoms. The reagents which add to the carbonyl group and to the ethylene linkage are, therefore, for the most part very different.

Hydrogenation. Aldehydes and ketones are both readily hydrogenated to the corresponding primary and secondary alcohols by the use of hydrogen and a catalyst.

$$CH_3CHO + H_2 \xrightarrow{\text{Catalyst}} CH_3CH_2OH$$

$$(CH_3)_2C = O + H_2 \xrightarrow{\text{Catalyst}} CH_3CHOHCH_3$$

This is the reversal of the process by which aldehydes and ketones may be prepared, and, at temperatures of about 200° in the presence of copper or nickel, there is a mobile equilibrium; with increasing temperature the dehydrogenation is favored.

$$R_2CHOH \underset{200°-300°}{\overset{\text{Catalyst}}{\rightleftharpoons}} R_2C = O + H_2$$

At room temperature, hydrogen and a suitable catalyst will hydro-

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genate aldehydes and ketones practically completely; above 200° the reverse reaction is evident. The aldehydes, ketones, and alcohols undergo other reversible reactions at still higher temperatures so that the dehydrogenation process (unlike the hydrogenation) is never quantitative.

Reduction. Hydrogen may also be added to the carbonyl group by using some reagent which liberates "nascent hydrogen." For example, zinc and acid, sodium and alcohol, or sodium amalgam and water are often employed. We shall use the symbol [H] for the hydrogen which comes from such reducing agents. These reagents usually reduce aldehydes and ketones to alcohols.

$$R_2CO + 2[H] \longrightarrow R_2CHOH$$

An effective reagent for the reduction of the carbonyl group of aldehydes and ketones is aluminum isopropoxide.

$$3RCHO + Al[OCH(CH_3)_2]_3 \longrightarrow (RCH_2O)_3Al + 3CH_3COCH_3$$

$$(RCH_2O)_3Al \xrightarrow{H_2SO_4} 3RCH_2OH + Al_2(SO_4)_3$$

This reducing agent is a specific reagent for aldehydes and ketones. It does not affect the carbon-carbon double linkage nor cause the replacement of a halogen atom by hydrogen. In most instances, hydrogen gas and a catalyst as well as the usual sources of "nascent hydrogen" are more general in their action. For example, the reduction of tribromo- or trichloroacetaldehyde with most reagents results in the formation of either acetaldehyde or ethyl alcohol. With aluminum isopropoxide, however, only the carbonyl group is reduced. The tribromoethyl alcohol, CBr_3CH_2OH, which is thus produced is used as an anesthetic under the name of *avertin*. The reaction may be written:

$$3CBr_3CHO + Al[OCH(CH_3)_2]_3 \longrightarrow (CBr_3CH_2O)_3Al + 3(CH_3)_2CO$$

$$(CBr_3CH_2O)_3Al \xrightarrow{H_2SO_4} 3CBr_3CH_2OH + Al_2(SO_4)_3$$

The aluminum isopropoxide is essentially a catalyst for the transfer of hydrogen from the secondary alcohol to the ketone or aldehyde. Indeed, aluminum *t.*-butoxide may be employed as the catalyst and other secondary alcohols besides isopropyl alcohol will then enter into a reaction with aldehydes or ketones. In solution at temperatures of 40° to 100°, the reaction slowly reaches an equilibrium. The composition of the equilibrium mixture depends on the nature of the carbonyl compound and the alcohol, the temperature and, of course, the concentration of factors and products. We may

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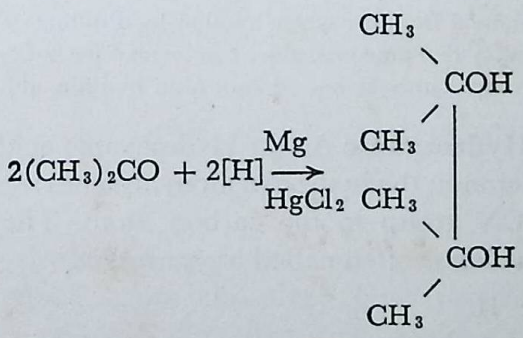
write the general equation for the reversible balanced reaction as

$$RCOR' + R_1CHOHR_2 \underset{\text{alkoxides}}{\overset{\text{Al}}{\rightleftharpoons}} RCHOHR' + R_1COR_2$$

There is an obvious analogy between this reversible reaction and the one written in the preceding section for the gaseous phase in the presence of a catalyst. In the presence of an aluminum alkoxide catalyst in solution, the two carbonyl compounds RCOR′ and R_1COR_2 compete for two hydrogen atoms. The energy relations are such that an aldehyde (R′ = H) reacts with a secondary alcohol, but will be essentially balanced if two ketones are involved (all R's = alkyl). Even a ketone may be reduced nearly quantitatively by isopropyl alcohol, however, if the boiling point of the desired product is much higher than acetone. A slow distillation removes the acetone and thus upsets the balanced equilibrium causing the reaction to proceed completely to the right.

$$\underset{\text{High-boiling ketone}}{RCOR} + \underset{\text{Isopropyl alcohol}}{(CH_3)_2CHOH} \xrightarrow[\text{as catalyst}]{\text{Al alkoxide}} \underset{\text{High-boiling secondary alcohol}}{RCHOHR} + \underset{\text{bp 56° Removed by distillation}}{CH_3COCH_3}$$

Dimolecular Reduction. Ketones can be also reduced to 1,2-dihydroxy compounds known as *pinacols* (see p. 205); this type of reduction involves the joining of two molecules and is called *dimolecular reduction.* It is accomplished by metals in alkaline solution; amalgamated magnesium is particularly effective.



The simplest representative, whose preparation from acetone is shown by the equation above, is called *pinacol.* Here, as elsewhere in organic chemistry, the name of the earliest known representative of a class of compounds has become the general name for the class.

Bisulfite Reaction. Ketones which contain one methyl group adjacent to the carbonyl group, and all aldehydes, combine with sodium bisulfite to form solid crystalline compounds soluble in water

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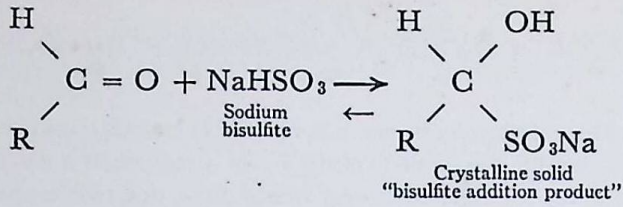
but insoluble in an excess of sodium bisulfite solution.



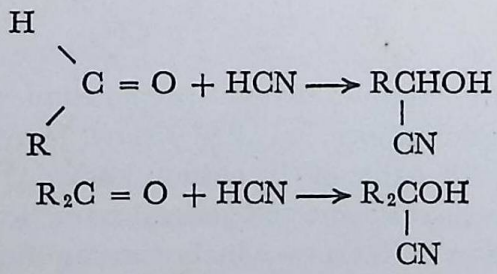
It is still unsettled whether in the bisulfite addition compound the sulfite group is linked to carbon through oxygen or sulfur.

Purification of Aldehydes and Methyl Ketones. On shaking an aldehyde with sodium bisulfite solution and cooling, a crystalline mass of the bisulfite addition product is formed which can be filtered. This reaction is utilized for purifying aldehydes and methyl ketones. The reaction is reversible, but the equilibrium is such that most of the material is present as the addition product; by using sufficient excess of bisulfite practically all of the aldehyde can be converted into the desired product, which can be further purified by recrystallization. To regenerate the aldehyde the addition product is warmed in water solution with a reagent which will react with sodium bisulfite. By removing the bisulfite in this way, the equilibrium is reversed completely and the aldehyde is set free. Two reagents which are used for this purpose are sodium carbonate and dilute hydrochloric acid. The reaction between a bisulfite addition product and sodium carbonate is shown in the equation which follows; the student should work out the corresponding equation for hydrochloric acid.

$$\underset{\underset{SO_3Na}{|}}{RCHOH} + Na_2CO_3 \xrightarrow[\text{(in } H_2O)]{} RCHO + Na_2SO_3 + NaHCO_3$$

The aldehyde is obtained from the water solution by distilling or extracting with an organic solvent. Exactly the same procedure can be used for purifying ketones which contain a methyl group. Other ketones do not form bisulfite addition products.

Addition of Hydrocyanic Acid. Hydrocyanic acid combines with aldehydes and ketones; the hydrogen atom attaches itself to the oxygen atom and the CN group to the carbon atom. The product is an hydroxynitrile which is often called a *cyanohydrin*.



Because hydrocyanic acid is so dangerous to handle, the cyanohydrins are often prepared by treating the bisulfite addition product with a solution of potassium

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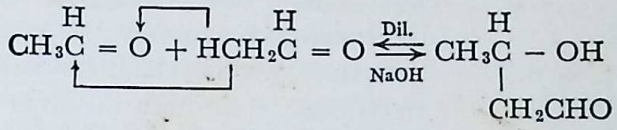
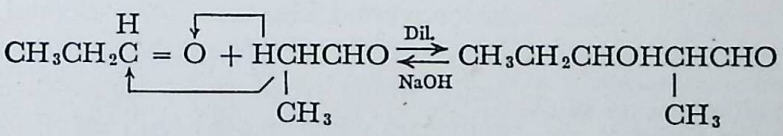
cyanide. A small amount of hydrocyanic acid is formed by the action of free sodium bisulfite on the potassium cyanide. This hydrocyanic acid then combines with the aldehyde which is in equilibrium with the bisulfite addition product. The equilibrium conditions are thereby upset and more bisulfite addition product dissociates to produce more free aldehyde and more free bisulfite; the latter further liberates free hydrocyanic acid which again combines with an equivalent amount of free aldehyde. In this way the reaction proceeds to completion without any large quantity of aldehyde or hydrocyanic acid ever being present in the reaction mixture.

Aldol Condensation. The addition reactions of the carbonyl group include a reaction in which one molecule of an aldehyde adds to the carbonyl group of another molecule. Such a reaction is called an *aldol condensation.* It is reversible and is brought about by the action of dilute alkali.



(The formula for the product has been written with a crooked chain to show the analogy between this reaction and other addition reactions of the carbonyl group.) The product formed from acetaldehyde is called *aldol*, $CH_3CHOHCH_2CHO$.

When the higher aldehydes are treated with dilute alkali, an aldol condensation takes place, but always in such a way that a hydrogen atom on the *carbon atom immediately adjacent to the carbonyl group* is involved. Thus, propionaldehyde reacts as follows:



If there is no hydrogen atom on the carbon atom next the carbonyl group, no aldol condensation takes place. Thus trimethylacetaldehyde, $(CH_3)_3CCHO$, forms no aldol when treated with dilute alkali.

When warmed with concentrated solutions of sodium hydroxide, all aldehydes which undergo the aldol condensation form brown sticky materials insoluble in water known as *resins.* These are probably produced by repeated aldol condensations until a very large molecule is formed. Ketones do not form resins under the same conditions.

Condensation of Ketones. Ketones undergo a self-condensation similar to the aldol condensation. For example, acetone in the pres-

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ence of an alkali yields **diacetone alcohol.**

$$(CH_3)_2C = O + CH_3COCH_3 \overset{Ba(OH)_2}{\rightleftharpoons} \underset{\text{Diacetone alcohol}}{(CH_3)_2COHCH_2COCH_3}$$

In this reaction the equilibrium is unfavorable for the product; only a few per cent of diacetone alcohol is formed when liquid acetone is treated with solid barium hydroxide. However, this difficulty is obviated in the manufacture of diacetone alcohol by a special device. The solid catalyst, $Ba(OH)_2$, is placed in a porous container above boiling acetone. The vapors are condensed in such a way that the liquid is returned to the boiler continuously by passing through the porous vessel which holds the catalyst. In its passage through the solid catalyst the liquid acetone is converted to diacetone alcohol as far as the equilibrium conditions permit (a few per cent). The diacetone alcohol being much less volatile than the acetone does not volatilize and accumulates in the boiler; since no catalyst is present, the concentration of product may greatly exceed the equilibrium conditions. In fact, in this way nearly all of the acetone may be converted into diacetone alcohol. It is interesting that this product, though perfectly stable when pure, immediately decomposes when treated with alkali forming the equilibrium mixture which is largely acetone. The apparatus used in this preparation (Fig. 7) is known as a *Soxhlet extractor* and is employed whenever a liquid is to be passed continuously through a solid as in the extraction of solid fatty material by ether.

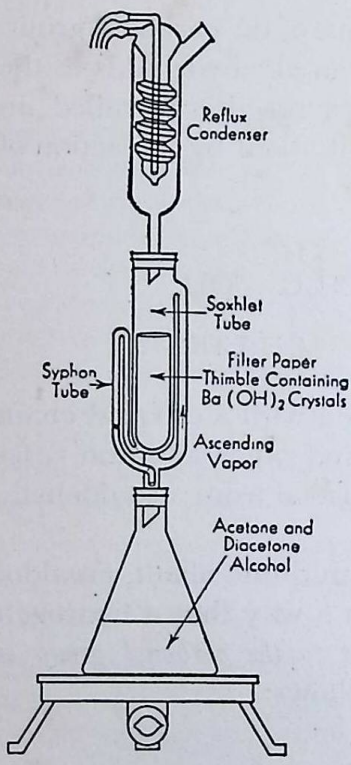

FIG. 7. Soxhlet extraction apparatus used in the conversion of acetone to diacetone alcohol.

The aldol condensation and the corresponding condensation of ketones are of interest because they represent a reaction, essentially balanced at room temperature, in which a carbon-carbon link is involved. The heat evolved is small (in the gas phase the formation of aldol from acetaldehyde is exothermic by about 5 kg-cal per mole) corresponding to a balanced reaction. In hydrocarbons, by contrast, the formation of a carbon-carbon link involves the liberation of considerable heat and the dissociation

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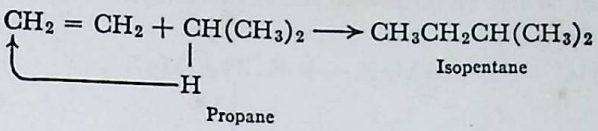
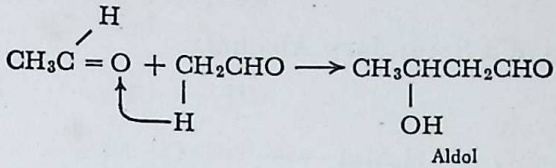
of a carbon-carbon link the absorption of considerable energy. For example the alkylation reactions (p. 62) are analogous to the aldol condensation in that in both reactions two molecules combine with the formation of a new carbon-carbon bond.





But it can be calculated from the heats of combustion that in the first reaction at 25° (if a catalyst could be found to operate at that temperature) the heat evolved would be 24 kg-cal. (Heats of combustion of ethylene + propane − isopentane = 337 + 530 − 843 = 24.) Corresponding to this large heat evolution we find that the equilibrium constant for the reaction calculated by accurate methods shows that no appreciable quantities of reactants would be in equilibrium with the product at 25°.

The energy changes are so different in the two reactions because in one a hydrogen atom adds to carbon while in the other it adds to oxygen. The same situation is found when a hydrogen molecule adds, on the one hand, to an ethylenic linkage and on the other to a carbonyl group; the hydrogenation of ethylene to ethane is exothermic by 33 kg-cal and the reduction of acetaldehyde to ethyl alcohol is exothermic by 13 kg-cal.

It is most important to realize that the considerations above apply only to the position of the equilibrium and have nothing to do with rates. But this is only half the story. As far as equilibria are concerned, such a reaction as the addition of methane to acetaldehyde would also be nearly balanced at room temperature; so too would aldol-like addition reactions in which the new carbon-carbon linkage involved carbon atoms far removed from the carbonyl group, the terminal CH_3 group in propionaldehyde, for example. Yet neither of these reactions takes place with any catalyst that has yet been found. The fact that the carbon atom *next* to the carbonyl group is involved in aldol condensations, and the fact that alkaline conditions cause the reaction to proceed rapidly, are closely connected and concern the mechanism by which the equilibrium is established. *Such facts cannot be predicted from energy relations.* Various explanations of these facts have been suggested, but they have not been sufficiently demonstrated to warrant consideration here.

Reaction with the Grignard Reagent. Both aldehydes and ketones combine with the Grignard reagent. The first product of the reaction is a magnesium compound which is easily hydrolyzed by water or decomposed by acids, yielding an alcohol. In this manner *aldehydes yield primary or secondary alcohols and ketones tertiary alcohols.* The reactions are illustrated by the following examples.

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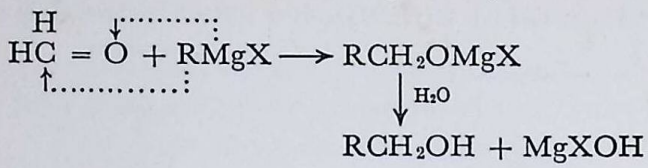
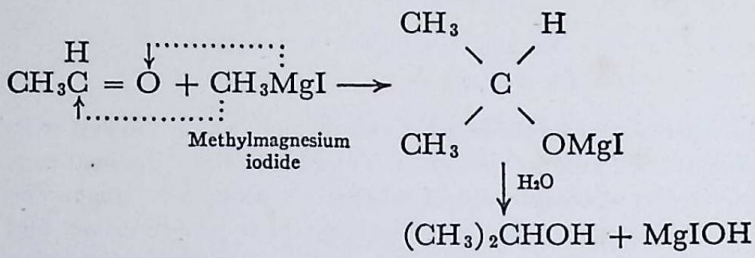
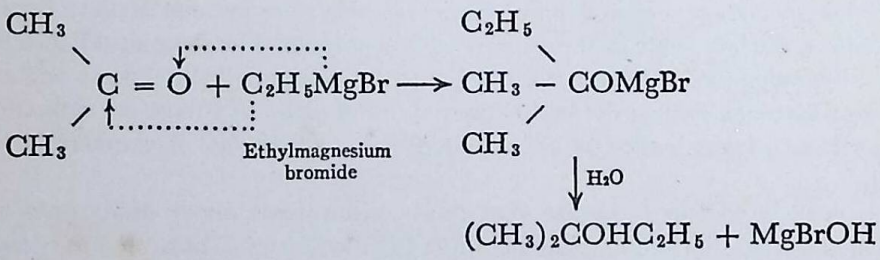
1. Synthesis of a Primary Alcohol. If *formaldehyde* (as a gas or sometimes as the solid polymer) is added to a Grignard reagent, the decomposition of the product yields a primary alcohol.



2. Synthesis of a Secondary Alcohol.



3. Synthesis of a Tertiary Alcohol.



Since a variety of primary, secondary, and tertiary alcohols can thus be prepared, these three reactions are of the greatest importance. It will be noted that in these reactions the magnesium atom together with the halogen atom attaches itself to oxygen, and the alkyl group goes to the carbon atom. These reactions proceed rapidly at room temperature in ether solution. They are usually carried out by preparing the Grignard reagent in ether solution as described in Chap. 2, and then slowly adding the aldehyde or ketone. The reaction mixture is then treated with ice-cold ammonium chloride solution or acid, which hydrolyzes the addition product and keeps the basic magnesium salt (MgXOH) in solution. Lithium alkyls (p. 29) may be used in place of the Grignard reagent in the above reactions.

A Summary of the Addition Reactions. In all the addition reactions of the carbonyl group except hydrogenation, we have been dealing with the addition of unsymmetrical reagents. It is important to remember the way in which such reagents add. A very simple rule

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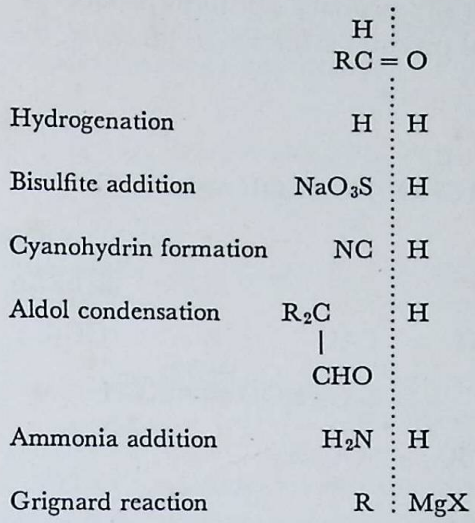
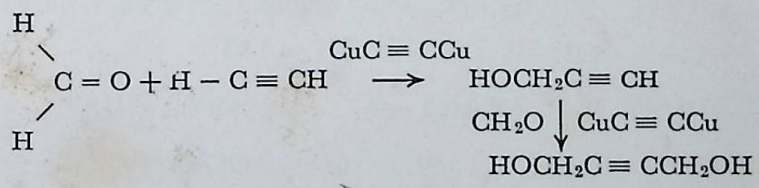
holds: *a hydrogen atom or a metal adds to the oxygen, the residue adds to the carbon.* All the reagents (except RMgX) are substances with an active hydrogen atom. The following diagram illustrates the addition reactions of aldehydes (all of these also take place with methyl ketones).



The *addition of ammonia* has been included in this diagram because there is evidence that aldehydes do combine with ammonia to give products of the type $RCHOHNH_2$ (called an *aldehyde ammonia*); but this reaction is usually followed by other reactions yielding complex products.

The addition of acetylene has been mentioned earlier (p. 68). In the presence of copper acetylide as a catalyst, acetylene will add to carbonyl compounds as $H - C \equiv CH$. The reaction with formaldehyde will serve as an illustration.



Reaction of Aldehydes with Alcohols. Alcohol and water might be added to the diagram given above since the addition compounds of the type $RCH(OH)_2$ and $RCH(OH)(OC_2H_5)$ are probably formed in aqueous

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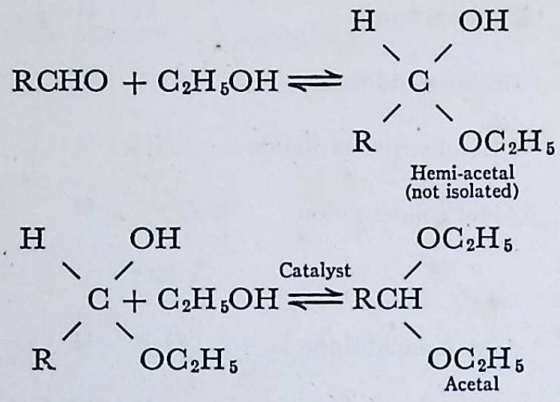
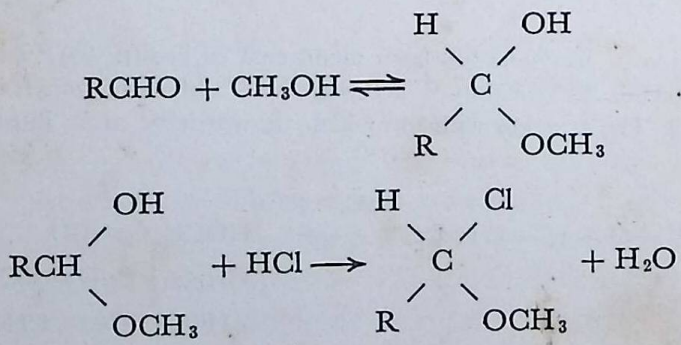
and alcoholic solutions of aldehydes. However, except for a few chloroaldehydes (p. 145) the products are too unstable to isolate. If an aldehyde is treated with an alcohol in the presence of calcium chloride or a trace of acid, a reaction takes place which probably proceeds through the primary addition product of the aldehyde and alcohol. The final product is known as an *acetal*, the intermediate as a *hemi-acetal*.



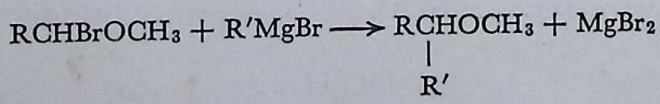
The acetals are hydrolyzed by boiling with aqueous acids; they are insensitive to bases.

When a mixture of an aldehyde and an alcohol is treated with an excess of hydrogen chloride or hydrogen bromide the product is an alpha halogen ether. The course of the reaction is probably as follows:



Thus **α-chloromethyl ether,** $ClCH_2OCH_3$, is made from formaldehyde, methyl alcohol, and hydrogen chloride.

Alpha halogenated ethers react readily with the Grignard reagent because of their highly reactive halogen. This reaction is utilized to prepare many higher ethers.



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Condensation with Ammonia Derivatives. It has been found that aldehydes and ketones react with derivatives of ammonia to form unsaturated compounds which in many instances are crystalline solids. If **hydroxylamine,** NH_2OH, is used, the compounds are called *oximes*, and if **phenylhydrazine,** $C_6H_5NHNH_2$, is used, the compounds are known as *phenylhydrazones*. With **semicarbazide,** $NH_2NHCONH_2$, **semicarbazones** are formed.

$$R_2C\boxed{O}+\underbrace{N\boxed{H_2}OH}_{\text{Hydroxylamine}} \rightleftharpoons \underbrace{R_2C=NOH}_{\text{An oxime}}+H_2O$$

$$R_2C\boxed{O}+\underbrace{C_6H_5NHN\boxed{H_2}}_{\text{Phenylhydrazine}} \rightleftharpoons \underbrace{R_2C=NNHC_6H_5}_{\text{A phenylhydrazone}}+H_2O$$

$$R_2C\boxed{O}+\underbrace{N\boxed{H_2}NHCONH_2}_{\text{Semicarbazide}} \rightleftharpoons \underbrace{R_2C=NNHCONH_2}_{\text{A semicarbazone}}+H_2O$$

Similar reactions occur with aldehydes and the products are known by the same general names. It is convenient to remember that these three reagents which condense with aldehydes and ketones have the general formula BNH_2, that the products from ketones have the general formula $R_2C = NB$, and the products from aldehydes the formula $RCH = NB$ (B is OH for the oximes, C_6H_5NH for the phenylhydrazones, and $NHCONH_2$ for the semicarbazones). It is often supposed that the condensation proceeds through the intermediate formation of an addition product $R_2COHNHB$ which then loses water; if so, these reactions may be thought of as a special case of the ammonia addition reaction mentioned above.

$$R_2CO + NH_2B \rightleftharpoons R_2{>}C\begin{matrix}OH\\ \diagup\\ \diagdown\\ NHB\end{matrix} \rightleftharpoons R_2C = NB + H_2O$$

Identification of Aldehydes and Ketones. The identification of very small amounts of liquids is always a very difficult matter in the laboratory. The identification of small amounts of solids is relatively easy if the solids have a melting point between room temperature and 200°. The simple aldehydes and ketones are all liquids, and the problem of identifying them therefore resolves itself into the problem of converting them into crystalline solids with sharp melting points.

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This is mostly done by means of one of the three condensation reactions just described. In fact hydroxylamine, phenylhydrazine, and semicarbazide are often called *carbonyl group reagents* because they form crystalline condensation products with most aldehydes and ketones. For the simplest aldehydes and ketones, the last two reagents are used since the oximes of low molecular weight are liquid. The phenylhydrazones and semicarbazones formed from practically all aldehydes and ketones are crystalline solids with a sharp melting point.

The reaction is usually carried out in aqueous solution or a mixture of alcohol and water if the carbonyl compound is insoluble in water. The reagent is usually added in the form of its hydrochloride. (Like ammonia, these reagents are bases and form salts with acids.) Since the reaction proceeds most rapidly in a solution whose acidity corresponds to that of one containing hydrochloric acid to which an alkali acetate has been added, sodium or potassium acetate is added in excess to react with the hydrochloric acid. The product separates as a crystalline solid, which causes the balanced reaction to go more nearly to completion. The entire reaction is thus represented by the following general equation.

$$R_2CO + BNH_2{\cdot}HCl + CH_3COOK \rightleftharpoons \underset{\text{Precipitate}}{R_2C = NB} + CH_3COOH + KCl$$

The composition of the equilibrium mixture and the speed with which equilibrium is attained depend on the aldehyde or ketone, the reagent, and the acidity of the solution. Under comparable conditions the condensation with ketones is less complete (at equilibrium) than with aldehydes. For this reason aldehydes may be used to regenerate ketones from their condensation products; acetic acid is used to accelerate the reaction.

$$R_2C = NB + RCHO \rightleftharpoons RCH = NB + R_2CO$$

Tests for Aldehydes. The fuchsine test and the reaction with ammoniacal silver nitrate are often used for distinguishing aldehydes from ketones. The fuchsine test consists of adding a solution of the material to a solution of *fuchsine* (magenta) which has been barely decolorized with sulfur dioxide; such a solution is known as *Schiff's reagent*. If an aldehyde is present, a bright pink color soon appears. Ketones do not give this test and do not reduce ammoniacal silver nitrate (p. 129).

REACTIONS INVOLVING HALOGEN

Replacement of Carbonyl Oxygen. The carbonyl oxygen in simple aldehydes and ketones may be replaced by the action of phosphorus pentachloride.

$$RCHO + PCl_5 \longrightarrow RCHCl_2 + POCl_3$$

$$R_2CO + PCl_5 \longrightarrow R_2CCl_2 + POCl_3$$

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The dichloro compounds thus produced undergo hydrolysis on boiling with alkali and regenerate the carbonyl compound.

Replacement of Hydrogen by Halogen. By the action of chlorine or bromine on a ketone, one or more hydrogen atoms adjacent to the carbonyl group are readily replaced by halogen.

$$CH_3COCH_3 + Br_2 \longrightarrow \underset{\text{Monobromoacetone}}{CH_2BrCOCH_3} + HBr$$

It is very interesting that the hydrogen atom replaced is the same one that is active in the aldol condensation. We thus see that as a general rule the hydrogen atoms on the *carbon adjacent to the carbonyl group* are active. This carbon atom is often called the *alpha* carbon atom since by one method of nomenclature the position of the substituent in aldehydes or ketones is denoted by Greek letters, thus;

$$\overset{\gamma}{C}H_3\overset{\beta}{C}H_2\overset{\alpha}{C}HBrCHO,$$ is known as *alpha bromobutyraldehyde.*

The halogen in α-bromoaldehydes or ketones can be replaced by hydrogen by treatment with a dilute solution of hydriodic acid at room temperature.

$$CH_3COCH_2Br + 2HI \longrightarrow CH_3COCH_3 + HBr + I_2$$

In practice an aqueous solution of potassium iodide is added to an alcoholic solution of the bromo compound which has been acidified with hydrochloric acid. The reaction is unusual in that it is quantitative and rapid. Since there are excellent volumetric methods for the determination of iodine, the reduction of an α-bromoaldehyde or ketone by hydriodic acid can be followed quantitatively.

The direct interaction of aldehydes and halogen leads to a mixture of products. The cyclic trimers (p. 131), however, can often be brominated with the replacement of only one hydrogen per carbonyl group. The alpha halogen ketones and aldehydes are reactive substances and are used in syntheses. They are extremely lachrymatory in their action and the bromoacetones are used as a "tear gas."

Chloral. Trichloroacetaldehyde, commonly called *chloral*, can be prepared by treating acetaldehyde with chlorine water or by the action of chlorine on ethyl alcohol. In the latter reaction, the chlorine first oxidizes the alcohol to acetaldehyde and then chlorinates this substance. Chloral is an oily liquid which boils at 97° and has the unusual property of combining with a molecule of water, forming the crystalline solid, **chloral hydrate,** $CCl_3CH(OH)_2$. This finds a limited use in medicine as an hypnotic.

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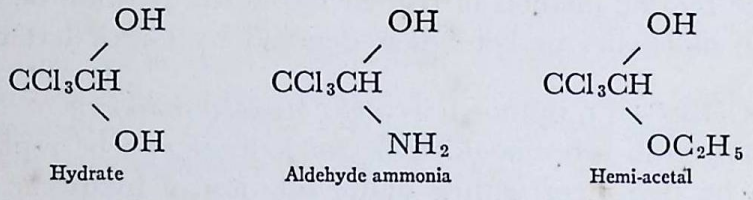
Chloral hydrate is of scientific interest because it appears to be one of the few stable compounds in which two hydroxyl groups are attached to the same carbon atom. It easily loses water on heating, forming the aldehyde. Some prefer to write the formula $CCl_3CHO \cdot H_2O$ instead of $CCl_3CH(OH)_2$, leaving it undecided as to whether a dihydroxy compound is really at hand. The fact that chloral hydrate does not affect Schiff's reagent whereas chloral does, is evidence in favor of the dihydroxy formula. Apparently the reaction between chloral and Schiff's reagent is faster than the hydration.

Chloral also combines with one molecule of alcohol to form a compound which is probably one of the few examples of a hemi-acetal (p. 142).



With one molecule of ammonia chloral gives a true aldehyde ammonia.

The Haloform Reaction. Chloral is rapidly decomposed on treatment with aqueous sodium hydroxide yielding chloroform, $CHCl_3$, and sodium formate.

$$CCl_3 \vdots CHO + NaO \vdots H \longrightarrow CHCl_3 + HCOONa$$

A similar reaction takes place with trichloroacetone, CCl_3COCH_3; here sodium acetate is one of the products.

$$CCl_3 \vdots COCH_3 + NaO \vdots H \longrightarrow CHCl_3 + CH_3COONa$$

This reaction is taken advantage of in preparing chloroform (p. 154). Sodium hypochlorite acts on *acetaldehyde or any methyl ketone* to form chloroform. It also acts on substances which are readily *oxidized to acetaldehyde or a methyl ketone*, since it is both an oxidizing agent and a chlorinating agent. The reactions proceed very rapidly and no intermediates can be isolated under these conditions.

Chloroform from alcohol:

$$CH_3CH_2OH + NaOCl \longrightarrow CH_3CHO + NaCl + H_2O$$
$$CH_3CHO + 3NaOCl \longrightarrow CCl_3CHO + 3NaOH$$
$$CCl_3CHO + NaOH \longrightarrow CHCl_3 + HCOONa$$

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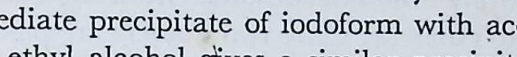
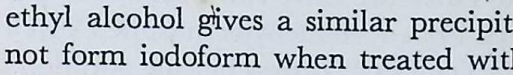
Chloroform from acetone:



$$CH_3COCH_3 + 3NaOCl \longrightarrow CH_3COCCl_3 + 3NaOH$$



$$CH_3COCCl_3 + NaOH \longrightarrow CH_3COONa + CHCl_3$$

A similar reaction occurs if sodium hypobromite (NaOBr) or sodium hypoiodite (NaOI) is used in place of the hypochlorite; the halogen-containing products are **bromoform,** $CHBr_3$, or **iodoform,** CHI_3. The latter is a yellow solid with a characteristic odor and is easily identified.

The action of one of these reagents on a methyl ketone is a convenient way of preparing an acid RCOOH from the *methyl ketone*, $RCOCH_3$.

The Iodoform Test for Ethyl Alcohol. Generally in the laboratory, sodium hypoiodite is prepared by treating an aqueous solution of iodine in an iodide with sodium hydroxide. Such a solution gives an immediate precipitate of iodoform with acetone, and when warmed with ethyl alcohol gives a similar precipitate. Since methyl alcohol does not form iodoform when treated with sodium hypoiodite, this test is often used *to distinguish ethyl from methyl alcohol*. Acetone, acetaldehyde, isopropyl alcohol and any substance which is a methyl ketone or is oxidized to a methyl ketone by hypoiodite will also give the test.

Structure of Acetaldehyde. The decomposition of chloral by sodium hydroxide to give chloroform and sodium formate is an important piece of evidence in regard to the structure of chloral and in turn of acetaldehyde itself. Chloroform must contain three chlorine atoms attached to the carbon atom (no other arrangement is possible), and, since it is easily formed from chloral, the group CCl_3 must also be present in this substance. Chloral, in turn, is formed by the replacement of three hydrogen atoms in acetaldehyde by three chlorine atoms; hence the group CH_3 must be present in acetaldehyde. We can thus write acetaldehyde, C_2H_4O, as $CH_3(CHO)$, without for the time being committing ourselves as to the nature of the group in parenthesis.

The preparation of acetaldehyde from ethyl alcohol and its easy reduction to this same substance is clear indication that the two carbon atoms are linked to each other and not through oxygen. The oxidation to acetic acid is also evidence of the same fact. The aldehyde contains no hydroxyl group since it does not form H_3PO_3 with PCl_3; therefore, the hydrogen and oxygen must be attached as follows:

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$$CH_3C\overset{H}{\diagup} - O \quad \text{or} \quad CH_3C\overset{H}{\diagup} = O$$

Our reasons for preferring the second formula with a double linkage are exactly those given in connection with the structure of ethylene (p. 49).

The Structure of Ethylene. It will be remembered that the formula $CH_3CH\diagup\!\!\diagdown$ or CH_3CH for ethylene was discarded (p. 50) because ethylene dichloride is CH_2ClCH_2Cl. We shall now consider the facts which show that the addition product of ethylene and chlorine is the α, β dichloro compound. We have just seen that acetaldehyde must have the structure $\begin{matrix} H \diagdown \\ CH_3 \diagup \end{matrix} C = O$; the dichloride formed by replacing the oxygen by two chlorine atoms must, therefore, be CH_3CHCl_2. This is an entirely different substance from the chloride made by adding chlorine to ethylene. Only two isomers are possible, therefore, since that prepared from acetaldehyde must be CH_3CHCl_2, the one from ethylene is CH_2ClCH_2Cl. If the chlorine addition product from ethylene had been identical with that formed from acetaldehyde and PCl_5, then the formula CH_3CH for ethylene would have been established. No such hydrocarbon has ever been prepared in spite of numerous attempts. Apparently, hydrocarbons with divalent carbon atoms are not stable.

A FEW INDUSTRIALLY IMPORTANT ALDEHYDES AND KETONES

A number of aldehydes and ketones are commercially available. Of these the most important are **formaldehyde, acetaldehyde,** and **acetone.** They were long prepared from methyl alcohol, ethyl alcohol, and acetic acid respectively. New and even cheaper methods of producing the last two have been discovered. The importance of acetaldehyde lies in the fact that from it a great variety of compounds may be prepared. We will postpone a discussion of this development until the next chapter.

Formaldehyde. This aldehyde is prepared by the oxidation of methyl alcohol by air in the presence of metallic silver or copper at a temperature of about 300°. The reaction is carried out by passing a mixture of the vapors of methyl alcohol and air through a tube containing copper gauze kept at the desired temperature. The issuing gases containing formaldehyde, water, and unchanged methyl alcohol

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are passed through water which dissolves the organic material. A 40 per cent water solution of formaldehyde is sold as **formalin.**

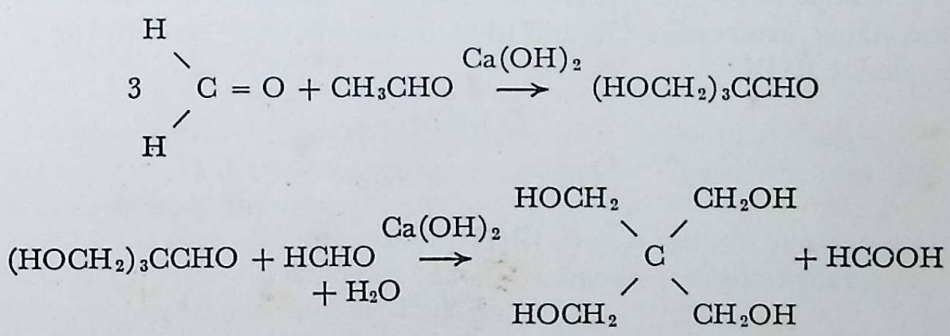
Large quantities of formaldehyde are prepared industrially for use as an antiseptic, as a starting point for the manufacture of other organic compounds, and for the preparation of synthetic resins (p. 515).[1] Formaldehyde solutions are used in preserving and hardening biological specimens. **Paraformaldehyde** (the polymer) is often used as a convenient source of the gas. Such solid paraformaldehyde is often heated in a little burner in order to disinfect a sickroom from contagious disease. Formaldehyde gas has a certain disinfecting action and kills the lower forms of life. This is one of the important uses of formaldehyde.

Unique Properties of Formaldehyde. As the first member of the series, formaldehyde has certain peculiarities. It differs from the other aldehydes in that on warming with concentrated sodium hydroxide it yields no resin, but undergoes the following reaction.

$$2HCHO + NaOH \longrightarrow CH_3OH + HCOONa$$

Reactions such as this where one molecule is oxidized at the expense of the other are known as *disproportionation* reactions. This particular reaction is known as the **Cannizzaro**[2] reaction; it is characteristic of those *aldehydes which have no hydrogen in the alpha position*, as R_3CCHO.

Formaldehyde also undergoes aldol condensations with other aldehydes. In these condensations all the alpha hydrogen atoms of the second aldehyde react, then a Cannizzaro reaction takes place between the product and excess formaldehyde. With acetaldehyde and formaldehyde this type of condensation leads to pentaerythritol.



[1] In 1940 the United States production of formalin was 90,000 tons; in 1944 it was 261,000 tons.

[2] Stanislao Cannizzaro (1826–1910), Professor of Chemistry in Rome. In addition to his work in organic chemistry, he played an important part in establishing clear ideas about atomic and molecular weights (1858).

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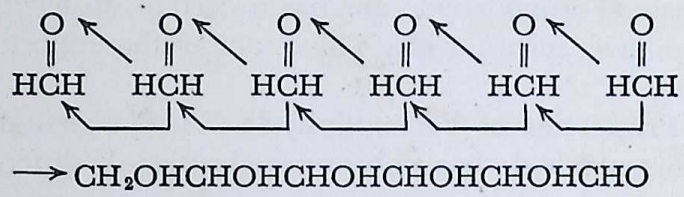
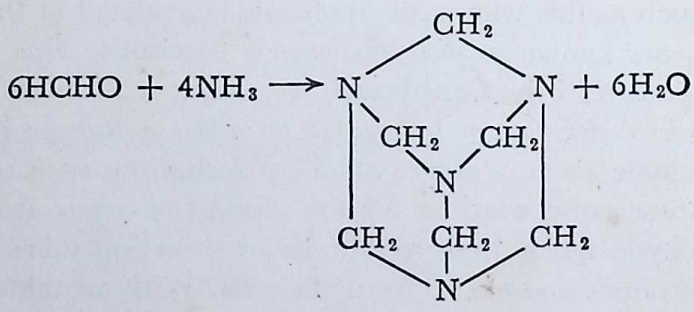
The nitric acid ester of pentaerythritol, $C(CH_2ONO_2)_4$, is the important high explosive PETN.

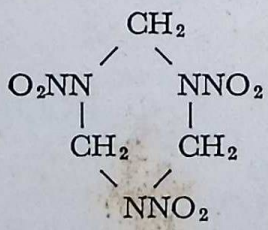
When a formaldehyde solution is kept slightly alkaline and allowed to stand, a condensation peculiar to formaldehyde takes place. A mixture of compounds known as *sugars* (carbohydrates) is formed. These are polyhydroxyaldehydes and ketones and contain five and six carbon atoms in a straight chain (Chap. 15). The actual product of the self-condensation of formaldehyde is a complex mixture, but the reaction may be illustrated by the following equation:



Hexamethylene tetramine, $(CH_2)_6N_4$, **hexamine,** is a complex substance obtained by evaporating a mixture of an aqueous solution of formaldehyde and ammonia:



The compound is a crystalline solid which is used in medicine under the name **urotropin.** On nitration it furnishes the powerful high explosive RDX.



Acetone. Acetone is the ketone most commonly met. Until 1927, it was prepared by the destructive distillation of calcium acetate which was obtained from the destructive distillation of wood.

It is now largely prepared by a special type of fermentation, and is

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a byproduct of the butyl alcohol industry (p. 16). A large amount of acetone is also made by the oxidation of isopropyl alcohol, which, as previously pointed out, is obtained from petroleum (p. 119).

The chief use of acetone industrially is as a solvent, since it dissolves many organic substances which dissolve even in alcohol with difficulty. The rapid growth of acetone as a commercial solvent may be illustrated by the fact that, while 6500 tons of acetone were manufactured in 1927, more than 100,000 tons were produced in 1940.

A COMPARISON OF ALDEHYDES AND KETONES

The following table summarizes the more important reactions of aldehydes and ketones. Formaldehyde is given a separate place, since as the first member of the series it has no alkyl group attached to the carbonyl group and has certain unique properties.

	Fehling's Solution	*Fuchsine Test*	*$NaHSO_3$*	*RMgX Yields*	
Formaldehyde	Oxidized	Positive	Addition product	Primary alcohol	Polymers of high mol. wt
Acetaldehyde and other aldehydes	Oxidized	Positive	Addition product	Secondary alcohol	Trimolecular polymers
Acetone and other ketones	No action	Negative	Addition product if CH_3COR	Tertiary alcohol	No polymer

QUESTIONS AND PROBLEMS

1. An ethylenic hydrocarbon $C_{10}H_{20}$ furnishes a single product on oxidation. This product does not add sodium bisulfite. What is the structural formula of the hydrocarbon?

2. Write structural formulas for heptanone-3, 2-methylbutanal, diethyl ketoxime, 2,3-dimethylheptanal, 3-methyl-octanone-4, acetaldehyde phenylhydrazone, the semicarbazone of butanone-2.

3. A sample of an organic liquid is either hexanal, methyl butyl ketone, butyric acid, or 1-chlorohexane. What chemical tests would you use to identify the liquid?

4. Write balanced equations for the following reactions: (*a*) methyl

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ethyl ketone and hydroxylamine, (*b*) hexanal and semicarbazide, (*c*) 2-ethylhexanal and phenylhydrazine.

5. How would you reduce $(CH_3)_2C{=}CHCHO$ to $(CH_3)_2C{=}CHCH_2OH$, and $C_2H_5COC_2H_5$ to $(C_2H_5)_2\underset{\underset{OH}{|}}{C} - \underset{\underset{OH}{|}}{C}(C_2H_5)_2$?

6. Show by means of equations that the liberation of an aldehyde from its bisulfite compound by either sodium carbonate or hydrochloric acid depends on the removal of sodium bisulfite from an equilibrium mixture.

7. Indicate the reactions you would use to prepare (*a*) dipropyl ketone and (*b*) dibutyl ketone from butyl alcohol.

8. Compare the behavior of pentanal, pentanone-2, and pentanone-3 with (*a*) sodium bisulfite, (*b*) dilute sodium hydroxide, (*c*) hydrogen cyanide, (*d*) ammoniacal silver nitrate, (*e*) Fehling's solution.

9. Write balanced equations for the following reactions: (*a*) CH_3MgI and CH_3COCH_3, (*b*) $(CH_3)_2CHMgBr$ and CH_3CH_2CHO, (*c*) $CH_3CH_2CH_2MgBr$ and CH_2O, (*d*) CH_3CH_2MgBr and $CH_3COCH_2CH_3$, (*e*) CH_3CH_2MgBr and H_2O.

10. How are formaldehyde and acetone prepared industrially, and what are their more important uses?

11. Define and illustrate the following terms: *acetal*, *hemiacetal*, *Cannizzaro reaction*, *haloform reaction*, *aldol condensation*.

12. Write equations (showing for each reaction the experimental conditions to be used) for preparing:

a. $CH_3CH_2CH_2CHO$ from $CH_3CH_2CH_2CH_2OH$
b. CH_3OCH_2Cl from CH_3OH
c. $CH_3CCl_2CH_3$ from $CH_3CHOHCH_3$
d. CH_3COCH_3 from CH_3CH_2OH
e. CH_3CHO from paraldehyde
f. $CH_3CH_2\underset{\underset{OH}{|}}{CH} - \underset{\underset{CH_3}{|}}{CHCHO}$ from CH_3CH_2CHO
g. CHI_3 from CH_3COCH_3

13. Outline a procedure for separating by chemical means a mixture of butanol, hexanal, and ethyl propyl ketone. Each of the three substances is to be recovered after the separation.

14. When 0.2640 g of a monobromoketone was treated with acidified potassium iodide it liberated 0.4061 g of iodine. What was the molecular weight of the bromoketone?

15. (Optional.) Compare the energy relations in the aldol condensation with those in the alkylation of olefins with paraffins. Can you explain the fact that the aldol condensation does take place at room temperature, while the alkylation does not?

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Chapter 8

THE POLYHALOGEN COMPOUNDS: DETERMINATION OF STRUCTURE AND SYNTHESIS OF SIMPLE COMPOUNDS: IMPORTANT INDUSTRIAL SYNTHESES

The polyhalogen derivatives of methane are listed below together with their physical properties. They are all heavier than water and insoluble in it. We shall study in detail a few of the more important polyhalogen compounds.

POLYHALOGEN DERIVATIVES OF METHANE

Name	*Formula*	*Melting Point*	*Boiling Point*
Methylenechloride (dichloromethane)	CH_2Cl_2	−97°	40°
Chloroform (trichloromethane)	$CHCl_3$	−63°	61°
Carbon tetrachloride	CCl_4	−23°	77°
Methylenebromide (dibromomethane)	CH_2Br_2	−53°	99°
Bromoform	$CHBr_3$	8°	151°
Carbon tetrabromide	CBr_4	91°	190°
Methyleneiodide (diiodomethane)	CH_2I_2	6°	181°
Iodoform	CHI_3	119°	
Carbon tetraiodide	CI_4	Sublimes between 90° and 100° *in vacuo*	

Carbon Tetrachloride. Carbon tetrachloride (tetrachloromethane) is prepared in enormous quantities by the action of **chlorine** on **carbon disulfide** which in turn is prepared in the electric furnace by heating coke and sulfur.

$$\underset{\text{Carbon disulfide}}{CS_2} + 3Cl_2 \longrightarrow CCl_4 + \underset{\text{Sulfur chloride}}{S_2Cl_2}$$

The two products of the chlorination of carbon disulfide can be separated by fractional distillation.

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Uses of Carbon Tetrachloride. Carbon tetrachloride is a volatile liquid which finds wide use because it is an incombustible solvent. It is one of the few organic substances which will not burn. Being heavier than water and insoluble in water, it can be used for extracting organic compounds from aqueous solution. It is now widely used in the dry cleaning of clothes; for this purpose it is often mixed with gasoline in such proportions that the mixture will not catch fire. Carbon tetrachloride is used in certain types of fire extinguishers which are particularly adapted for fires which occur in chemical laboratories or in connection with burning oil. When water is poured on oil fires, it tends to spread a layer of burning oil. Carbon tetrachloride, on the other hand, volatilizes; the heavy gas hangs as a smothering cloud over the fire and extinguishes it. Carbon tetrachloride is used in the treatment of animals suffering from internal parasites.

Preparation of Chloroform. Chloroform (trichloromethane) can be prepared by reducing carbon tetrachloride with iron and water.

$$CCl_4 + [H] \xrightarrow{\text{Iron + water}} CHCl_3 + HCl$$

The older method of manufacture consists in distilling ethyl alcohol or acetone with sodium hypochlorite solution or a suspension of bleaching powder (p. 146).

Uses of Chloroform. Chloroform, like carbon tetrachloride, is noninflammable and an excellent solvent and, although expensive, is used in the laboratory and in the industries for this purpose. It is also used to a limited extent as an anesthetic. For this purpose it must be pure and kept in completely filled brown bottles, since, in the presence of light and air, it undergoes decomposition to some extent forming the poisonous carbonyl chloride, $COCl_2$ (p. 326), and hydrochloric acid. Commercial chloroform always contains a small amount of ethyl alcohol which prevents the formation of carbonyl chloride.

Chemical Reactions of Chloroform. On hydrolysis with alkali, chloroform yields formic acid; the "ortho acid," $CH(OH)_3$, which is perhaps formed first, is not stable (p. 101).

$$CHCl_3 + 3KOH \longrightarrow HCOOH + 3KCl + H_2O$$

It will be recalled, however, that the esters of orthoformic acid are stable (p. 101); these result when chloroform is treated with a sodium alkoxide. For example, sodium ethoxide yields the ethyl ester of

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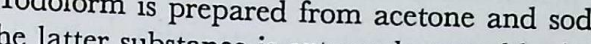
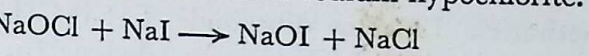
orthoformic acid.

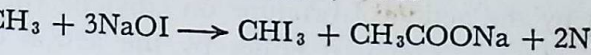


$$CHCl_3 + 3NaOC_2H_5 \longrightarrow CH(OC_2H_5)_3 + 3NaCl$$

Iodoform. Iodoform is prepared from acetone and sodium hypoiodite. Since the latter substance is extremely unstable, it is made as it is needed from sodium iodide and sodium hypochlorite.



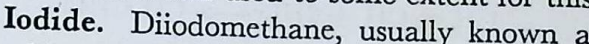
$$NaOCl + NaI \longrightarrow NaOI + NaCl$$



$$CH_3COCH_3 + 3NaOI \longrightarrow CHI_3 + CH_3COONa + 2NaOH$$

Iodoform is a yellow solid which melts at 120° and has a characteristic odor. It was used in the early development of antiseptic surgery as a dressing for wounds and is still used to some extent for this purpose.

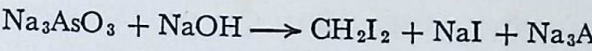
Methylene Iodide. Diiodomethane, usually known as *methylene iodide*, is prepared by the reduction of iodoform. The best reagent for this purpose is sodium arsenite; this rather unusual reducing agent gives an almost quantitative yield.



$$CHI_3 + Na_3AsO_3 + NaOH \longrightarrow CH_2I_2 + NaI + Na_3AsO_4$$

Methylene iodide is a colorless liquid boiling at 181° and having a density of 3.3. With the exception of mercury it is the heaviest liquid known.

Dichlorodifluoromethane. The only fluorine derivative of the paraffin hydrocarbons having industrial importance is dichlorodifluoromethane, CCl_2F_2, a gas which boils at −30°. The commercial significance of this substance lies in the fact that it is an ideal refrigerant. For refrigerators and for air-conditioning units, it is far superior to ammonia, sulfur dioxide, and ethyl chloride in that it is practically odorless, nontoxic, noninflammable, and noncorrosive. Dichlorodifluoromethane is manufactured from carbon tetrachloride by a rather special process.



$$3CCl_4 + 2SbF_3 \xrightarrow{SbCl_5} 3CCl_2F_2 + 2SbCl_3$$

HALOGEN DERIVATIVES OF ETHANE AND OTHER HYDROCARBONS

Isomeric Dichloroethanes. The two isomeric dichloroethanes, **ethylene dichloride,** CH_2ClCH_2Cl, and **ethylidene chloride,** CH_3CHCl_2, were mentioned in the last chapter in connection with the structures of ethylene and acetaldehyde (p. 148). The former is prepared from ethylene and chlorine (p. 49) and is produced indus-

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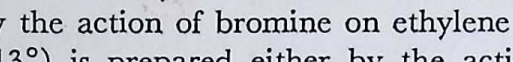
trially for use as a solvent. It is a liquid, insoluble in water, and boiling at 84°. The isomeric chloride (bp 59°) results from the action of phosphorus pentachloride on acetaldehyde.

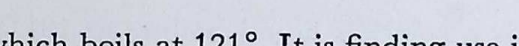


$$CH_3CHO + PCl_5 \longrightarrow CH_3CHCl_2 + POCl_3$$

Dibromoethanes. Ethylene dibromide, CH_2BrCH_2Br (bp 131°), is prepared by the action of bromine on ethylene (p. 57), while its isomer (bp 113°) is prepared either by the action of phosphorus pentabromide on acetaldehyde or by the addition of hydrobromic acid to acetylene.

$$CH \equiv CH + 2HBr \longrightarrow CH_3CHBr_2$$

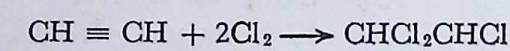
Tetrachloroethylene. Tetrachloroethylene is obtained as a by-product of the manufacture of chloroform from carbon tetrachloride.



$$2CCl_4 + 2Fe \longrightarrow CCl_2 = CCl_2 + 2FeCl_2$$

It is a liquid which boils at 121°. It is finding use in place of carbon tetrachloride in the treatment of internal parasites in animals.

Acetylene Tetrachloride. This substance is prepared by the action of chlorine on acetylene.



$$CH \equiv CH + 2Cl_2 \longrightarrow CHCl_2CHCl_2$$

The reaction is almost explosive unless the gases are brought together in the presence of some inert solid material. Acetylene tetrachloride (symmetrical tetrachloroethane) is a liquid which boils at 147°. It is a valuable solvent for cellulose acetate (p. 299) and other organic compounds.

Nomenclature of Polyhalogen Compounds. A general method of naming the halogen derivatives of the hydrocarbons is necessary, since the higher members of the series have many isomers. Thus, while trichloromethane can only mean $CHCl_3$ (chloroform), trichloropropane might be any one of five isomers. The method commonly employed considers the substances as derivatives of the corresponding paraffin hydrocarbons and denotes by Greek letters the position of the substituting atoms. The number, name, and position of the halogen atoms come first, and the name of the parent hydrocarbon last. The following examples will make this clear.

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$\underset{\gamma}{CH_3}\underset{\beta}{CH_2}\underset{\alpha}{CHCl_2}$ α,α-dichloropropane

$\underset{\gamma}{CH_3}\underset{\beta}{CHCl}\underset{\alpha}{CH_2Cl}$ α,β-dichloropropane

$\underset{\gamma}{CH_2Cl}\underset{\beta}{CH_2}\underset{\alpha}{CH_2Cl}$ α,γ-dichloropropane

The Greek letters are written under the above formulas to indicate the method; they are usually written only in the name. The lettering should always begin from the most substituted end of the molecule (which, of course, may be either at the right or the left depending on how the formula is written). The method of naming compounds with different halogen atoms is shown below:

$CH_2ClCHBrCH_3$ α-chloro-β-bromopropane

$CH_2ClCHBrCH_2I$ α-chloro-β-bromo-γ-iodopropane

or α-iodo-β-bromo-γ-chloropropane

The Geneva method of naming the polyhalogen compounds is now preferred by many people. The compounds are named from the longest straight-chain paraffin hydrocarbon, and the position of the substituent halogen atoms indicated by numerals in the usual way. Thus $CH_3CH_2CHCl_2$ is 1,1-dichloropropane, $CH_3\underset{\underset{CH_3}{|}}{C}HCHClCHBrCH_3$, is 2-methyl-3-chloro-4-bromopentane, and $CH_2ClCH_2CH_2CHClCH_3$, is 1,4-dichloropentane.

General Methods of Preparing Polyhalogen Compounds. The halogen derivatives of methane and ethane which have just been discussed are peculiar in that the halogen atoms must be on the same or adjacent carbon atoms. With compounds containing many carbon atoms we have a great variety of halogen compounds. These substances are often very useful in organic syntheses, since they will enter into many metathetical reactions. Irrespective of the length of the carbon chain we may summarize the methods of preparing dichloro and dibromo compounds as follows:

1. *Two halogen atoms on the same carbon atom.* Such compounds are prepared from aldehydes or ketones by the action of phosphorus pentachloride or pentabromide.

2. *Two halogen atoms on adjacent carbon atoms.* Such compounds are formed by the addition of chlorine or bromine to an olefin.

3. *Two halogen atoms on carbon atoms removed by one or more carbon atoms.* These compounds are prepared from the corresponding hy-

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droxy compounds (Chap. 10) by reactions exactly similar to those used in preparing alkyl halides from alcohols.

DETERMINATION OF STRUCTURE AND SYNTHESIS OF SIMPLE COMPOUNDS

In the previous chapters we have considered a variety of organic compounds and discussed methods for their preparation and some of their typical reactions. By means of such information the organic chemist is able to determine the structure of new compounds and to outline a procedure for their synthesis. The actual problems which confront the investigator today are too complex, for the most part, to be considered in the first course in the subject. The methods used in attacking these problems, however, are exactly like those employed in determining the structure of simple compounds.

There are two ways of determining the structure of an organic compound. We may study its physical properties and chemical reactions or we may attempt to synthesize it by reactions which lead to products of established structure. Usually both methods are used in such a way as to complement each other. An example will illustrate the methods and their use.

Let us consider first a liquid of unknown structure which, from qualitative and quantitative analyses and molecular-weight determinations, has the molecular formula $C_6H_{14}O$. Since a paraffin hydrocarbon with six carbon atoms would have the formula C_6H_{14}, our unknown must be a saturated compound. The saturated compounds containing one oxygen atom per molecule which we have had are ethers or alcohols. We therefore try some reaction which will distinguish between these two possibilities. Our unknown reacts readily with methylmagnesium iodide to form methane (p. 28). Therefore the unknown was an alcohol, $C_6H_{13}OH$, and not an ether.

Now we have to determine the structure, not of an unknown compound, but of a saturated alcohol. Let us heat it with sulfuric acid (p. 52). This treatment yields a hydrocarbon, C_6H_{12}. The hydrocarbon when ozonized (p. 61) furnishes acetaldehyde and butyraldehyde. We can now write a structural formula for the hydrocarbon: it is hexene-2, and the reaction with ozone is

$$CH_3CH_2CH_2CH = CHCH_3 \xrightarrow[\text{water and zinc dust}]{\text{Ozone, then}} CH_3CH_2CH_2CHO + CH_3CHO$$

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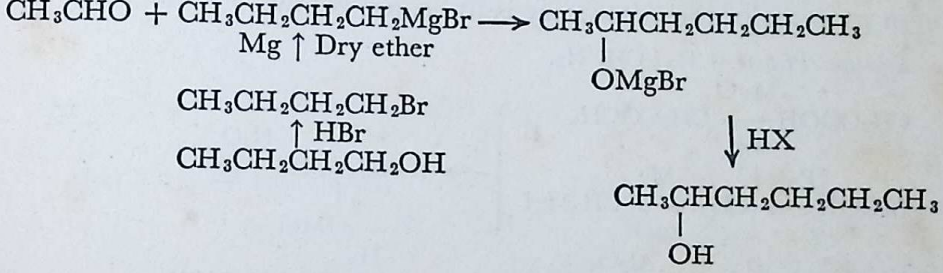
We have determined the structure of the dehydration product, and this limits the structure of our original alcohol to

$$CH_3CH_2CH_2CH_2CHOHCH_3 \text{ (I) or } CH_3CH_2CH_2CHOHCH_2CH_3 \text{ (II).}$$

Both these alcohols and only these two alcohols would furnish hexene-2 on dehydration. We can now either carry out additional reactions with the unknown which will distinguish between I and II, or we can synthesize the alcohols I and II and compare them with the unknown. In practice our course would be determined by the amount of the unknown at our disposal and by the length and difficulty of the syntheses. Let us assume that we have decided on the synthesis.

We have two methods of synthesizing secondary alcohols: the reduction of ketones, and the action of a Grignard reagent on an aldehyde. Let us choose the latter and concentrate our attention on the synthesis of I. To prepare this alcohol we could treat acetaldehyde with *n*-butylmagnesium bromide, or treat *n*-butyraldehyde with methylmagnesium iodide. Since acetaldehyde is the more readily available of the two aldehydes we will use it. The synthesis is then as follows:



The hexanol-2 obtained from the synthesis we compare in physical properties with our unknown alcohol. If there is agreement we complete the identification by taking a melting point of a mixture of a solid derivative of hexanol-2 and the unknown alcohol; the ester, for example, of the alcohol and an acid of high molecular weight.

We may assume that the synthetic hexanol-2 was identical with our original unknown alcohol. The problem we set ourselves, the determination of the structure and the synthesis of that unknown, has been solved. If the synthetic hexanol-2 were not identical with the unknown, then we would synthesize II, hexanol-3, and compare it with the unknown.

Now let us look back over the procedure we have followed. We first determined to what homologous series our unknown belonged by the

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application of class reactions: alcohols evolve gas on treatment with methylmagnesium iodide while ethers do not. There are many of these class reactions: ethylenic hydrocarbons add bromine whereas paraffins do not; aldehydes reduce ammoniacal silver solutions while simple ketones do not. The class reactions furnish much useful information quickly. Familiarity with them is part of the working knowledge of the organic chemist. Next we determined the exact structure of the unknown by specific reactions and by synthesis. Reactions and synthesis are the face and reverse of the same coin. Familiarity with the reactions of the different classes of organic compounds is also part of the working knowledge of the organic chemist.

Problems involving the determination of structure and the synthesis of organic compounds offer one of the best ways of reviewing the reactions of organic compounds and of acquiring skill in interpreting the meaning of the reactions. Problems of this sort will be found at the end of the chapters from this point on in the text. A few examples of syntheses follow.

Synthesis of a Paraffin. The synthesis of isobutane from the common reagents of the laboratory is indicated below.

Problem: Prepare $(CH_3)_2CHCH_3$.

$$\left.\begin{array}{l} CH_3COOH \xrightarrow[300^\circ]{MnO} CH_3COCH_3 \\ CH_3OH \xrightarrow{P+I} CH_3I \xrightarrow[\text{Ether}]{Mg} CH_3MgI \end{array}\right\} \longrightarrow (CH_3)_2\underset{\underset{OMgI}{|}}{C}CH_3 \xrightarrow{H_2O}$$

$$\longrightarrow (CH_3)_2COHCH_3 \xrightarrow[200^\circ]{Al_2O_3} (CH_3)_2C = CH_2 \xrightarrow[\text{Catalyst}]{H_2} (CH_3)_2CHCH_3$$

The student should note the mental process by which, working *backward step by step*, such a synthesis can be evolved. These backward steps may be summarized as follows: isobutane is a saturated hydrocarbon; saturated hydrocarbons can be made by (1) the reduction of unsaturated hydrocarbons and (2) from the Grignard reagent and water. Different routes will be traveled according to whether the first or second method is chosen. The first route has been selected in the example above. The unsaturated hydrocarbon is best prepared by loss of water from the corresponding alcohol, which is either tertiary butyl alcohol, $(CH_3)_3COH$, or the primary alcohol, $(CH_3)_2CHCH_2OH$. Tertiary alcohols in turn are made by the action of the Grignard reagent on ketones. This problem then resolves itself into the preparation of acetone and methylmagnesium iodide.

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Lengthening a Carbon Chain. Among the many problems which the organic chemist has to solve in synthetic work is that of making compounds having more carbon atoms than the one from which he starts. The following diagrams show how this can be done when one wants an alcohol or an acid.

Problem: Synthesize RCH_2OH *from* ROH.

$$ROH \xrightarrow[\text{or } P+I]{HX} RX \xrightarrow[\text{Ether}]{Mg} RMgX \xrightarrow{HCHO} RCH_2OMgX \xrightarrow{H_2O} RCH_2OH$$

Problem: Synthesize an acid RCOOH *from an alcohol* ROH.

$$ROH \xrightarrow[\text{or } P+I]{HX} RX \xrightarrow[\text{Ether}]{Mg} RMgX \xrightarrow{CO_2} RCOOMgX \xrightarrow[\text{(acidify)}]{} RCOOH$$

Alternative method.

$$ROH \xrightarrow[\text{or } P+I]{HX} RX \xrightarrow{KCN} RCN \xrightarrow{NaOH} RCOONa \xrightarrow{HX} RCOOH$$

Problem: Synthesize an acid RCH_2COOH *from an acid* RCOOH.

$$RCOOH \xrightarrow{C_2H_5OH} RCOOC_2H_5 \xrightarrow[Na + C_2H_5OH]{[H]} RCH_2OH \xrightarrow{P+I} RCH_2I \xrightarrow{Mg} RCH_2MgI \xrightarrow{CO_2} RCH_2COOH$$

Alternative for last two steps, prepare RCH_2CN *and hydrolyze.*

Two carbon atoms may be added in a single reaction by treating a Grignard reagent with ethylene oxide.

$$RMgX + \underset{\diagdown\ \diagup}{CH_2 - CH_2}\,O \longrightarrow RCH_2CH_2OMgX$$

$$RCH_2CH_2OMgX + H_2O \longrightarrow RCH_2CH_2OH + MgXOH$$

Limitations of the Reactions. These synthetic methods which we have generalized above by the use of the symbol R for an alkyl group, *are subjected to serious limitations in practice.* A consideration of these limitations is the province of an advanced course in organic chemistry. As an example of such limitations, we may mention the fact that certain highly branched ketones, such as $(CH_3)_3CCOC(CH_3)_3$, will

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not react with the Grignard reagent, or react abnormally. In general, the *branching of the chain* near the functional group and the introduction of reactive groups (halogen, OH, NH_2, etc.) modify the reactions greatly. Increasing the length of the chain as a rule has little disturbing influence; hence the general methods of synthesis give good results where primary alkyl groups are attached to the reacting group.

IMPORTANT INDUSTRIAL SYNTHESES

We have already considered several important industrial methods of preparing organic compounds, particularly from the simpler hydrocarbons. We are now in a position to survey the over-all picture of the industrial sources of the simpler aliphatic compounds such as the alcohols, the acids, and the carbonyl compounds. Basically the cheap sources of raw materials are (1) carbohydrates, (2) petroleum, (3) natural gas, and (4) coke. There are many methods of going from almost all these sources to the individually important aliphatic compounds. The choice of the method to be employed is a matter of cost. An important element in this cost is the transportation either of the raw material or the finished product. For this reason one process suitable in an area where petroleum or natural gas occurs plentifully (and hence is very cheap) is replaced by another process in a locality where coal is much cheaper than oil or gas. Still another raw material may be used if both electricity and coal are cheap. Carbohydrates are usually a more expensive source of carbon compounds than either petroleum, gas, or coal; but ethyl alcohol has been prepared in the United States by the fermentation of molasses from Cuba in competition with ethyl alcohol from natural gas. Where the products must be used in beverages or foods, of course, other considerations than cost come into play.

Synthetic Acetaldehyde. Cheap acetaldehyde is a substance of great industrial importance although relatively small quantities of it are sold. It is instead converted on the spot into such substances as ethyl alcohol, acetic acid, acetic anhydride, aldol, ethyl acetate, and acetone. Acetaldehyde can be prepared from acetylene, from ethyl alcohol (and this from either ethylene or carbohydrates), and by oxidation of petroleum hydrocarbons such as propylene, propane, ethane, and butane. Using an excess of hydrocarbon vapor and air at 500°, considerable amounts of acetaldehyde, formaldehyde, and methyl alcohol are formed. Methane is but little affected under these conditions.

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Acetaldehyde from Acetylene. Acetaldehyde is prepared by passing acetylene into a vigorously agitated suspension of mercuric sulfate in dilute sulfuric acid. The temperature of the reaction mixture is somewhat above room temperature, and the acetaldehyde (bp 20°) distills as rapidly as it is formed. By suitable condensers and fractionating columns it can be separated from the excess acetylene and obtained very pure.

An examination of the formulas of acetylene and acetaldehyde makes it evident that the formation of one from the other involves the addition of a molecule of water. There are several steps in the actual reaction, and both the acid and the mercuric sulfate are catalysts for the process.

$$CH \equiv CH + H_2O \xrightarrow[\text{dil. } H_2SO_4]{HgSO_4} CH_3CHO$$

Sources of Acetylene. Acetylene is prepared in enormous quantities from calcium carbide and water (p. 65). Calcium carbide in turn is manufactured by heating lime and coal (or coke) in an electric furnace. Hence acetylene is a very cheap substance where hydroelectric power is available. Very recently large-scale experiments have been in progress looking to the production of acetylene by the thermal cracking of the simple paraffin hydrocarbons at very high temperatures (1000° to 1500°). Not only ethane and propane, but methane itself forms acetylene at these very high temperatures. The thermal exposure must be very short or the acetylene will undergo other reactions; hydrogen is the other product.

$$C_2H_6 \xrightarrow{1500^\circ} HC \equiv CH + 2H_2$$

$$2CH_4 \xrightarrow{1500^\circ} HC \equiv CH + 3H_2$$

It is interesting that these reactions at *room temperature* are endothermic by very large amounts, namely 73 and 90 kg-cal respectively. Corresponding to these large values, the equilibrium constants at 25° are enormously in favor of methane and ethane. Parallel with the large heat involved, the equilibrium shifts in favor of the product rapidly as the temperature rises; but only at very high temperatures is acetylene formed in appreciable quantities because the equilibrium is so unfavorable at room temperature.

Syntheses Based on Acetylene. The use of acetylene as a raw material for chemical syntheses has been extensively exploited in Germany; less so in the United States. We may expect, however, to

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see an increase in the use of acetylene in this country because of the variety of important materials that can be prepared from it. Some of the important synthetic reactions of acetylene have already been mentioned. They may be profitably reviewed and amplified here.

The addition of alcohols to acetylene in the presence of alkoxide catalysts furnishes alkyl vinyl ethers.

$$HC \equiv CH + CH_3OH \xrightarrow{NaOCH_3} \underset{\text{Methyl vinyl ether}}{CH_2 = CHOCH_3}$$

These ethers may be polymerized, or they may be hydrogenated to mixed saturated ethers, or they may be hydrolyzed to furnish acetaldehyde and regenerate the alcohol.

$$CH_2 = CHOCH_3 + H_2 \xrightarrow{\text{Catalyst}} CH_3CH_2OCH_3$$

$$CH_2 = CHOCH_3 + H_2O \xrightarrow{H^+} CH_3CHO + CH_3OH$$

This last reaction offers a synthesis of acetaldehyde competitive with the direct addition of water to acetylene described on page 67.

The addition of an aliphatic acid to acetylene in the presence of the zinc or cadmium salt of the acid can be controlled so that either 1 or 2 moles of acid will add. The product from the addition of 1 mole of acetic acid, vinyl acetate, is the material from which polyvinyl acetate is prepared. The product from 2 moles of acetic acid is a source of acetic anhydride (see page 166).

$$CH_3COOH + HC \equiv CH \xrightarrow{Zn(OCOCH_3)_2} CH_3COOCH = CH_2$$

The reaction between acetylene and water, which was described previously as furnishing acetaldehyde, can be run under different experimental conditions to furnish acetone.

$$2HC \equiv CH + 3H_2O \xrightarrow{ZnO} CH_3COCH_3 + CO_2 + H_2$$

Acetylene will also add to carbonyl compounds as H— and —C ≡ CH. This reaction with formaldehyde permits the synthesis of butadiene.

$$2H_2C = O + HC \equiv CH \xrightarrow[\text{acetylide catalyst}]{\text{Metallic}} HOCH_2C \equiv CCH_2OH$$

$$\xrightarrow[Ni]{H_2} HOCH_2CH_2CH_2CH_2OH \longrightarrow CH_2 = CH - CH = CH_2$$

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Acetic Anhydride from Acetaldehyde. The oxidation of acetaldehyde to acetic acid or its reduction to ethyl alcohol requires no special comment (the latter process cannot at present compete with other ways of preparing alcohol). The transformation of acetaldehyde to acetic anhydride, however, involves a new reaction.

By oxidizing acetaldehyde with air in a dilute solution in an unreactive volatile solvent such as carbon tetrachloride or benzene, a mixture of acetic acid and acetic anhydride is formed directly. The reaction appears to involve the formation of a *per*acid (an unstable acyl derivative of hydrogen peroxide). This peracetic acid then reacts with acetaldehyde to give acetic anhydride and water.

$$CH_3CHO + O_2 \longrightarrow \underset{\text{Peracetic acid}}{CH_3\overset{\overset{O}{\|}}{C} - O - O - H}$$

$$CH_3\overset{\overset{O}{\|}}{C} - O - O - H + CH_3CHO \longrightarrow (CH_3CO)_2O + H_2O$$

The products of the reaction, acetic anhydride and water, of course react to form acetic acid. But, in the presence of a diluent, the rate of hydration of acetic anhydride is low because the concentration of the two reactants is low. Therefore, only a portion of the anhydride is converted into the acid before the mixture is separated by distillation. The volatile diluent, unchanged aldehyde, and water are removed continuously by distillation; the acetic acid and anhydride are then separated by distillation. The dehydration of acetic acid is an endothermic reaction and takes place only at very high temperatures; the oxidation of acetaldehyde is a strongly exothermic reaction. Through the intermediary of a peracid the two reactions—oxidation and dehydration—are in a sense *coupled* together so that the over-all reaction proceeds to completion only slightly above room temperature.

Acetic Anhydride from Acetic Acid. Acetic anhydride is used in very large amounts for preparing cellulose acetate (p. 299). In the acetylation of cellulose, 1 mole of acetic acid is formed for every mole of anhydride consumed (the reaction is similar to the reaction of an alcohol and an anhydride, p. 89). Industry is, therefore, confronted with the problem of reconverting large quantities of acetic acid to the anhydride. This can be done in many different ways. We have already noted two: the use of sulfur chloride or a high-temperature dehydration. Two other methods follow.

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When acetylene is passed into acetic acid containing a metallic catalyst, a compound is formed which yields acetic anhydride and acetaldehyde on heating.

$$HC \equiv CH + 2CH_3COOH \xrightarrow{\text{Catalyst}} \underset{\text{Ethylidene diacetate}}{CH_3CH(OCOCH_3)_2}$$

$$CH_3CH(OCOCH_3)_2 \xrightarrow{\text{Heated}} (CH_3CO)_2O + CH_3CHO$$

Acetone on heating to a temperature of 650° to 700° undergoes thermal decomposition forming methane and a highly unsaturated compound, *ketene*, $CH_2 = C = O$.

$$CH_3COCH_3 \xrightarrow{650°-700°} CH_2 = C = O + CH_4$$

Ketene (p. 323) forms acetic anhydride when it is passed into acetic acid.

$$CH_2 = C = O + CH_3COOH \longrightarrow (CH_3CO)_2O$$

The acetone for ketene manufacture can be cheaply prepared by the dehydrogenation of isopropyl alcohol, which in turn is made from propylene from natural gas or the gases from petroleum cracking. Acetone can also be made from acetylene as outlined earlier in this chapter. The preparation of acetone from acetic acid was described earlier. Where petroleum or natural gas is available, however, this method of manufacture is hardly competitive.

Other Products from Acetaldehyde. In the presence of aluminum ethoxide, $Al(OC_2H_5)_3$, acetaldehyde is converted to ethyl acetate.

$$2CH_3CHO \xrightarrow{Al(OC_2H_5)_3} CH_3COOCH_2CH_3$$

By means of the aldol condensation an unsaturated aldehyde (crotonaldehyde) can be formed from acetaldehyde. Subsequent catalytic reduction of this yields synthetic normal butyl alcohol. It is claimed that butyl alcohol can be prepared as cheaply by this series of reactions as by the fermentation process.

$$CH_3CHO + CH_3CHO \xrightarrow[\text{NaOH}]{\text{Dil.}} CH_3CHOHCH_2CHO$$

$$\downarrow \text{Heat, Catalyst}$$

$$CH_3CH_2CH_2CH_2OH \xleftarrow[\text{Catalyst}]{H_2} CH_3CH = CHCHO$$

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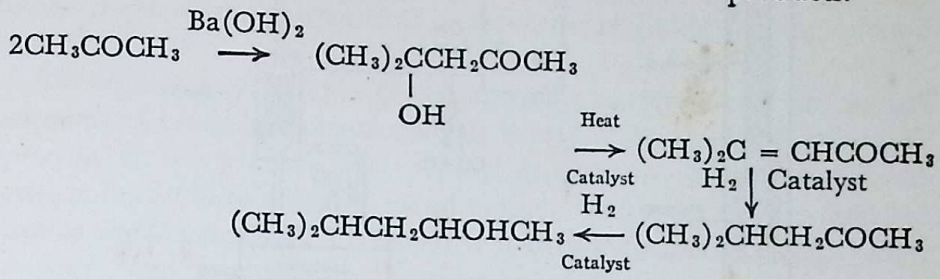
By a similar set of transformations acetone yields diacetone alcohol, mesityl oxide, and on hydrogenation methyl isobutyl ketone and methyl isobutyl carbinol. These are now commercial products.



SYNTHESES FROM CARBON MONOXIDE

The discussion up to this point has dealt with syntheses from coal or coke via acetylene. We now shall consider some important syntheses that start from carbon monoxide, which is prepared from coke by the water gas reaction.

$$H_2O + C\ (\text{coke}) \xrightarrow{1000^\circ} CO + H_2$$

Methane is a very cheap source of carbon in many parts of this country and hence is a promising source of carbon monoxide. At high temperatures with steam, methane forms carbon monoxide and hydrogen.

$$CH_4 + H_2O \xrightarrow[800^\circ\text{–}1000^\circ]{\text{Catalyst}} CO + 3H_2$$

In Europe, however, where there are no petroleum and natural gas deposits, coke from coal is of course the source of carbon monoxide.

Industrial Synthesis of Methyl Alcohol. A very large fraction of the methyl alcohol now prepared industrially is the product of the hydrogenation of carbon monoxide.

$$CO + 2H_2 \xrightarrow[\substack{300^\circ\text{–}400^\circ \\ \text{High pressure (200 atm)}}]{\text{Catalyst}} CH_3OH$$

The hydrogenation of carbon monoxide is a strongly exothermic reaction at 25°. Therefore, according to the rule previously given, the equilibrium constant at room temperature corresponds to a very large predominance of the product over the factors. Actually no equilibrium can be measured under these conditions. According to Le Chatelier's principle, raising the temperature favors the reverse reaction. Therefore a catalyst is desired which will work at as low a temperature as possible. High pressures obviously favor the formation of methyl alcohol.

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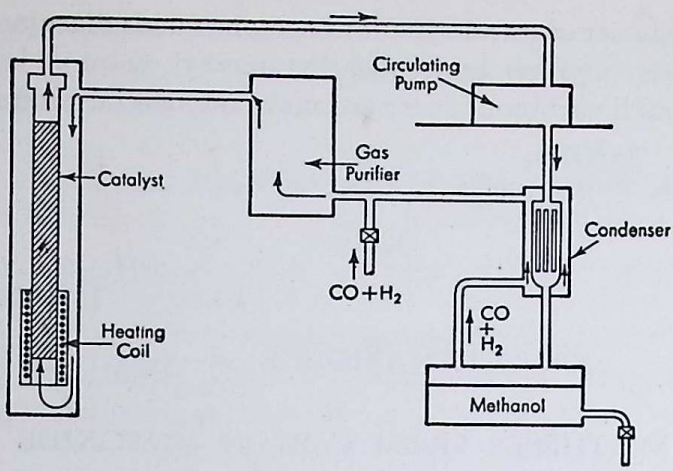

FIG. 8. Diagram showing the essential features of an apparatus for the synthesis of methyl alcohol from carbon monoxide and hydrogen.

Other Products from Carbon Monoxide. With a suitable catalyst, methyl alcohol and carbon monoxide under pressure yield acetic acid. Therefore this acid as well as methyl alcohol can be synthesized industrially from coal via carbon monoxide.

$$CH_3OH + CO \xrightarrow[\text{High pressure; above 300°}]{\text{Catalyst}} CH_3COOH$$

It has been found that, in addition to methyl alcohol, higher alcohols, such as propyl and isobutyl alcohols, are obtained in the catalytic hydrogenation of carbon monoxide. These products are probably formed by the interaction of two alcohol molecules with loss of water.

Such a process could repeat itself until a long-chain alcohol was formed. The following hypothetical mechanism would lead to the formation of higher alcohols.

$$CH_3OH + HCH_2OH \xrightarrow[\text{High pressure; 300°}]{\text{Catalyst}} CH_3CH_2OH + H_2O$$

$$CH_3CH_2OH + HCH_2OH \longrightarrow CH_3CH_2CH_2OH + H_2O$$

The hydrogenation of carbon monoxide may be carried out in the presence of catalysts which so favor the formation of longer chain compounds that these become the major product. These alcohols on dehydration yield unsaturated hydrocarbons which can be hydrogenated or alkylated to give the desired components of modern gasoline. In this way liquid fuels have been prepared commercially

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from coal via carbon monoxide. This process, developed in Germany before World War II and known as the *Fischer-Tropsch method*, was one of the two methods employed by that country to prepare gasoline without recourse to petroleum which was available in only limited amounts.

The other process by which Germany supplemented her small supplies of crude petroleum during World War II was the Bergius process. In this process, which is a hydrogenation of coal, powdered coal is mixed with a heavy metal catalyst and with the residual tar from a previous charge. The mixture is then hydrogenated under high pressure and temperature. Distillation of the product furnishes a gasoline fraction, a higher boiling gas oil fraction, and a tarry residue which is used in the next charge.

HEAT OF REACTION AND EQUILIBRIUM CONSTANTS

The industrial processes we have been considering in this chapter and which were considered in Chap. 6 illustrate how, by variations in temperature and pressure, certain reactions may be brought about. We have been concerned not only with conditions which cause a reaction to run rapidly, but also with conditions under which the equilibrium is in favor of the desired product. We have called attention to the fact that equilibrium constants may be calculated from thermal data alone (including specific heat data). These calculations involve a knowledge of physical chemistry beyond the scope of this book. However, it is possible to estimate roughly the order of magnitude of equilibrium constants at different temperatures from a knowledge of the heat of reaction. The essentially qualitative information thus obtained will help a student understand modern organic chemistry. He must bear in mind, however, that we are not concerned with differences which correspond to a 20 per cent or an 80 per cent conversion, but with differences between equilibria in which measurable quantities of factors or products are present and those in which a reaction runs to essential completion.

The student must also remember that the rules to be given for estimating the equilibrium constant apply to reactions in which all the factors and products are organic compounds or water. If polar substances like acids or ions take part in the reactions, complications result which may invalidate the simple rules here formulated. Furthermore, since a change of state (solid to liquid or liquid to gas, or the reverse) involves the absorption or evolution of heat, generalizations

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based on one physical state of reactants and products may not hold for another state.

For those reactions in which the same numbers of molecules are involved on both sides of the equation, the value of the equilibrium constant parallels the heat of reaction rather closely. Thus we may say for reactions of the types $A \rightleftharpoons B$ or $A + B \rightleftharpoons C + D$ (the reactants and products being in the same state) that when the heat evolved is greater than 12 kg-cal the equilibrium constant will correspond to an equilibrium mixture in which less than a millionth of a per cent of the factor (or factors) will be present. In other words, the reaction appears to go completely to the right. If the reaction is only slightly exothermic or endothermic, the equilibrium constant corresponds to an appreciably balanced reaction; i.e., an equilibrium mixture in which at least a few tenths of a per cent of all the components are present. Two examples of such balanced reactions with very small heat evolution have been encountered already. In one, the isomerization of the paraffin hydrocarbons, there was one molecule on each side of the equation; in the other, the esterification of an alcohol by an acid, there were two molecules on each side.

Where there are different numbers of molecules on the two sides, different rules apply. Thus, for reactions of the type $A + B \longrightarrow AB$ (addition reactions), or the reverse $AB \longrightarrow A + B$ (dissociation reactions), the relation between the heat of the reaction and the value of the equilibrium constant is more complicated. The following rule is a useful approximation: if the reaction $A + B \longrightarrow AB$ (all gases) is exothermic by more than 20 kg-cal at 25° and 1 atm pressure, the equilibrium constant corresponds to an essentially complete addition reaction (concentration of A and B less than 0.03 per cent). If the reaction is less exothermic than 20 kg-cal per mole, the equilibrium may correspond to appreciable quantities of factors and product, and if it is less exothermic than 10 kg-cal, almost certainly will. Further, if the reaction is only slightly exothermic (a few kilogram-calories), or is endothermic, the equilibrium constant at 25° and 1 atm will represent a mixture containing very little of the product. In other words, if the heat of the reaction $A + B \longrightarrow AB$ is essentially zero at 25°, the dissociation of AB into $A + B$ will be great under equilibrium conditions, provided a catalyst can be found.

A few applications of the above rule to reactions of the type $A + B \longrightarrow AB$ will be sufficient to show its usefulness; they also serve to emphasize the fact that all such estimates only show what will

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happen *if a catalyst is found which produces rates high enough for equilibrium to be attained.* In the hydrogenation of all the alkyl derivatives of ethylene which are known, the heat evolution at 25° is at least 26 kg-cal. Therefore no appreciable dissociation of a paraffin hydrocarbon into the unsaturated hydrocarbon and hydrogen can take place at room temperature whatever catalyst is employed. The reverse reaction (decomposition) being strongly endothermic is favored by rise of temperature; but, since the equilibrium is so far to the right at 25°, a relatively high temperature is required for appreciable decomposition (see the formation of acetylene above and p. 163). The hydrogenation of aldehydes and ketones, however, is somewhat different. Here the reaction $A + H_2 \longrightarrow AH_2$ (where A is an aldehyde or ketone and AH_2 an alcohol) is exothermic by only 10 to 16 kg-cal. (except formaldehyde where the value is 20). Following the rule, these relatively low values mean that the equilibrium constant will probably correspond to a measurable concentration of carbonyl compound and hydrogen in equilibrium with the alcohol at 1 atm pressure and 25° (assuming an active catalyst). As a practical matter the catalytic hydrogenation of aldehydes and ketones goes to completion at room temperature, but at a few hundred degrees the reverse reaction is very evident (p. 124). The gross differences in the temperatures required for the practical dehydrogenation of alcohols and paraffin hydrocarbons is due to the difference in the order of magnitude of the heat evolved in the hydrogenation reaction. In all hydrogenations and dehydrogenations, hydrogen is assumed to be in the gaseous state, and the generalizations hold if *both* the saturated and unsaturated compound are in the *same state* (gas or liquid).

The addition of water to an unsaturated hydrocarbon is another reaction which is exothermic but not strongly so. Here, one must watch carefully as to the physical state of the reactants and products including water, since the heat of vaporization of water is high. For the reaction of ethylene with water we find, from heats of combustion, an evolution of only 10 kg-cal at 25° in the gaseous state. Following the rule, we find that accurate calculations show the equilibrium mixture at 25° would contain an appreciable quantity of ethylene and water though alcohol would predominate; with the complex derivatives of ethylene the equilibrium becomes less favorable so that a number of hydroxyl compounds on treatment with acid catalysts form water and the unsaturated compounds. It should be noted, however, that in this reaction, unlike hydrogenation and dehydrogenation, the catalysts

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required at 25° are substances which also enter into other reactions; e.g., the acid catalysts will form esters. Furthermore, other dehydrations, such as ether formation, may take place more rapidly than the formation of a hydrocarbon. Probably a true equilibrium system involving ethylene, water, and alcohol can only be obtained in the vapor phase with a solid catalyst like aluminum oxide at temperatures considerably above 100°.

The alkylation and dealkylation (thermal decomposition) of hydrocarbons is similar to the addition and loss of water. For example, the reaction between methane and ethylene to yield propane is exothermic by 19 kg-cal at 25°. The equilibrium constant corresponds to less than 0.03 per cent dissociation of propane into the factors at 25° and 1 atm, assuming a catalyst for such a dissociation at this temperature could be found. Other combinations of hydrocarbons show about the same value; the reaction is somewhat less exothermic than hydrogenation, but more exothermic than hydration. We find, therefore, that considerably higher temperatures are required for appreciable decomposition of the paraffin hydrocarbons (even under the most favorable catalytic condition) than are required with the alcohols.

The following table summarizes some of the important generalizations that have just been discussed.

RELATION OF HEATS OF REACTIONS AND EQUILIBRIUM CONSTANTS

The figures given are for reactions in which the factors and products are in the same state, i.e., all gases or liquids or solids.

1. Reactions with the same numbers of molecules of reactants and products.

Rearrangement $A \longrightarrow B$

Heat evolved $>$ 6 kg-cal at 25° $K > 10^4$ at 25°
Example: Maleic to fumaric acid (p. 314).

Heat evolved a few kg-cal at 25° $K = 10^{-2}$ to 10^2 at 25°
Example: Butane $\rightleftarrows$ isobutane (all gases)

Reactions $A + B \longrightarrow C + D$

Ether formation $2CH_3OH \rightleftarrows CH_3OCH_3 + H_2O$ (all gases)
Heat evolved *ca.* 7 kg-cal $K = 10^6$.

Ester formation $RCOOH + R'OH \rightleftarrows RCOOR' + H_2O$
(all gases)
Heat evolved very slight at 25° $K = 10^{-2}$ to 10^2

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2. Reactions with different numbers of molecules of reactants and products.

$$A + B \rightarrow AB$$

Hydrogenation of ethylene derivatives (all gases)

Heat evolved *ca.* 25 kg-cal at 25° $K > 10^{10}$ at 25°

Hydrogenation of carbonyl compounds (all gases)

Heat evolved 10–16 kg-cal at 25° $K = 1$ to 10^3 (except CH_2O)

Alkylation of ethylene derivatives $CH_4 + CH_2{=}CH_2 \longrightarrow CH_3CH_2CH_3$

Heat evolved, all as gases, *ca.* 20 kg-cal at 25° $K = 10^7$

Hydration of ethylene derivatives

Heat evolved, all as gases, 5–10 kg-cal at 25° $K = 10^{-2}$ to 10^2

Aldol condensation

Heat evolved, all as liquids, 2–10 kg-cal at 25° $K = 10^{-3}$ to 10^2

[See p. 137. Depending on slight changes in structure, the hydroxyl compound or the carbonyl compound may predominate in equilibrium mixtures. The shift in K is, however, only a few powers of ten between the two extremes.]

Hydration of unsaturated ketones and aldehydes of the type $RCH = CHCOR$ Heat evolved, all as liquids, a few kg-cal at 25° $K = 10^{-1}$ to 10^{-4}

3. Decompositions with rearrangement

$$AB \longrightarrow A' + B'(CH_3)_2\underset{\underset{OH}{|}}{C} - \underset{\underset{OH}{|}}{C}(CH_3)_2 \longrightarrow (CH_3)_3CCOCH_3 + H_2O$$

Regarded as an addition reaction (reverse pinacone rearrangement) $A' + B' \longrightarrow AB$, the heat evolved, all as liquids, is ± 2 kg-cal. $K = 10^{-3}$ to 10^{-6}. The reaction in the sense $AB \longrightarrow A' + B'$ runs to completion.

Calculations of Heats of Reaction. If the student wishes to estimate the heat of a reaction from the usual tables of heats of combustion he must bear in mind the physical state of the products and the factors. The heats of combustion usually refer to the substance in the state in which it is present at 25° and 1 atm pressure. Where the compounds are not given as gases, the heat of vaporization must be added to the heat of combustion if data for the gaseous state are desired. Furthermore, if water enters into the reaction, it must be remembered that the heats of combustion are based on the formation of *liquid* water. In most calculations this fact is of no significance as water cancels out of the thermochemical reactions; but, if water itself is involved, a correction must be applied to obtain data for the gaseous state. The following reaction illustrates this simple but important fact. The heats of combustion

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of gaseous methyl alcohol and methyl ether are respectively 182.6 kg-cal and 347.6 kg-cal. This means that the following equations may be written.

$$2CH_3OH(g) + 3(O_2)(g) \longrightarrow 2CO_2(g) + 4H_2O(l) + 365.2 \text{ kg-cal}$$

$$CH_3OCH_3(g) + 3(O_2)(g) \longrightarrow 2CO_2(g) + 3H_2O(l) + 347.6 \text{ kg-cal}$$

Subtracting the second equation from the first we find that

$$2CH_3OH(g) - CH_3OCH_3(g) = H_2O(l) + 17.6 \text{ kg-cal}$$

Rearranging the equations:

$$2CH_3OH(g) \longrightarrow CH_3OCH_3(g) + H_2O(l) + 17.6 \text{ kg-cal}$$

(The letters in parenthesis after the formulas show the physical state referred to.) If, now, one wants to obtain the value of the heat of reaction with all the products in the gaseous state one must subtract the heat required to vaporize 1 mole of water, namely 10 kg-cal. Therefore we may write the following equation:

$$2CH_3OH(g) \longrightarrow 2CH_3OCH_3(g) + H_2O(g) + 7.6 \text{ kg-cal}$$

If one wishes to obtain the value for the heat of the reaction where all the products as well as the reactants are liquids one must subtract twice the heat of vaporization of methyl alcohol from, and add the heat of vaporization of dimethyl ether and water to the heat given in the last equation.

$2CHO_3H$	(1) $\longrightarrow$ $2CH_3OH$	(g) $- 2(8.4)$	Heat absorbed in vaporization
CH_3OCH_3	(g) $\longrightarrow$ CH_3OCH_2	(1) $+ 4.8$	Heat evolved in condensation
H_2O	(g) $\longrightarrow$ H_2O	(1) $+ 10.0$	Heat evolved in condensation

These added to the equation $2CH_3OH(g) \longrightarrow CH_3OCH_3\ (g) + H_2O\ (g) + 7.6$ kg cal give the desired value:

$$2CH_3OH\ (1) \longrightarrow CH_3OCH_3\ (1) + H_2O\ (1) + 5.6 \text{ kg-cal}$$

Not only must the physical state be considered in order to obtain the correct values of the heat of reaction from the heats of combustion, but the physical state has significance in comparing related reactions. By and large the energy changes in a given type of reaction in the gas state (and therefore the equilibrium constants) vary regularly in an homologous series or with isomeric changes in structure. But the energy changes involved in condensation and, above all, in dissolving in or mixing with a solvent are irregular so that small changes in structure may have surprising effects. This in turn means that in *solution* the equilibrium constant of a reaction may shift in an irregular manner with changes in structure of one of the reactants. This is particularly true if we are dealing with solids. For we have already seen that, while boiling points in an homologous series show regularity, melting points are much more erratic; and while heats of vaporization show simple regularities, heats of fusion do so to a lesser extent. This is likewise true of the energy changes involved in dissolving solids in liquids as compared with the mixing of a liquid with a solvent. Since the organic chemist and, especially, the biochemist are particularly interested in the behavior of solid substances in solution, they must proceed with caution in using calculations of equilibrium

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which apply to a reaction in the gaseous state (vapor phase). For all thesereasons it is very difficult to calculate accurately significant equilibrium constants for reactions in solution, but the order of magnitude is rarely affected by a change in state of all the factors and products.

Reactions Involving Unfavorable Equilibria. In the preparation of diacetone alcohol, we saw a reaction which could be completed in the laboratory in spite of an unfavorable equilibrium. Such examples are relatively rare in the laboratory, but are extremely important in industry. Where large quantities of material are to be prepared it is profitable to arrange the complicated apparatus usually necessary to cycle a reaction mixture over a catalyst and to separate the product after each pass. The student may recall the use of such a procedure in the synthesis of ammonia from nitrogen and hydrogen. Gaseous reactions are particularly adapted to cycling of this type. At first sight it would seem that in the presence of a suitable catalyst any reaction, however unfavorable the equilibrium, could be carried out in practice by such a procedure. On further consideration, however, it is evident that, if on each pass only a minute fraction of a per cent of product was obtained, the number of cycles would be so great that the time and cost would be prohibitive. Also in most processes side reactions enter in, so that other products are formed instead of the desired material if in each cycle there is not a considerable conversion.

For reactions of the type $A + B \longrightarrow AB$ where increased pressure forces the reaction to the right, unfavorable equilibrium (as measured at 1 atm) can be overcome by modern methods of operating at very high pressures. But here again there are limits to what may be accomplished, as is illustrated by the possibility of preparing acetaldehyde from carbon monoxide and methane. Calculations from heats of combustion show that at 25° the reaction, $CH_4 + CO \longrightarrow CH_3CHO$, is slightly *endothermic*. The decomposition of acetaldehyde to methane and carbon monoxide is slightly exothermic; it takes place under the catalytic influence of ultraviolet light. Accurate calculations of the equilibrium constant using thermal data and specific heats show that a pressure of 10^8 atm would be required to force the reaction in favor of aldehyde by as much as a per cent. Since the reaction is only slightly endothermic, not much would be gained by raising the temperature. At 700°, 10^6 atm would still be required. Since such pressures are out of the question, the search for a suitable catalyst is not of practical interest.

QUESTIONS AND PROBLEMS

1. What would be the effect on the position of the equilibrium and on the rate of the following reaction of (*a*) increasing the temperature, and (*b*) increasing the pressure?

$$C + H_2O \rightleftharpoons CO + H_2 + 29 \text{ kg-cal}$$

2. Name the following compounds: $CH_2BrCH_2CHCl_2$, $CH_3CHClCH_2Br$, CH_3CHCl_2, $CHCl_2CHCl_2$, $CH_3CHBrCH_2I$.

3. What substances will yield iodoform on treatment with sodium hypoiodite?

4. What is a coupled reaction?

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5. Show how acetaldehyde can be obtained from carbohydrates, or coal, or petroleum.

6. What is ketene? How is it prepared and what is its industrial importance?

7. An organic compound has the molecular formula $C_7H_{14}O$. It forms an oxime, but does not add sodium bisulfite. It adds two atoms of hydrogen on treatment with hydrogen and a metallic catalyst to form $C_7H_{16}O$. This latter compound on heating with sulfuric acid loses a molecule of water to furnish C_7H_{14}. The hydrocarbon C_7H_{14} on oxidation yields propionic acid and butyric acid. What is the structure of the original compound $C_7H_{14}O$?

8. Given methyl and ethyl alcohols, ether, and any necessary inorganic reagents, show how you would prepare:

(*a*) $CH_3CH_2CH_2OH$, (*b*) $(CH_3)_3COH$, (*c*) $CH_3CH_2CH_2CH_2COCH_2CH_3$, (*d*) $CH_3C(OH)(C_2H_5)_2$, (*e*) $CH_3CH_2CHOHCH_2CH_3$, (*f*) $CH_3CH_2CHClCHClCH_3$.

9. What reactions would you use to distinguish between $CH_3CHOHCH_3$, $CH_3COCH_2CH_2CH_3$, and $CH_3CH_2COCH_2CH_3$?

10. Write equations for the reactions involved in the preparation of chloroform from ethyl alcohol.

11. Assuming that hydroelectric power is available, outline a procedure for preparing at low cost the following compounds: acetone, ethylene chloride, acetic anhydride, butyl acetate.

12. Write equations for the reactions you would use to distinguish between $(CH_3)_3CCHO$ and $CH_3CH_2CH_2CH_2CHO$.

13. How would you convert

a. CH_3CH_2CHO to $CH_3CH_2CH_2CH(CH_3)_2$

b. $CH_3COOC_2H_5$ to C_2H_5OH

c. CH_3CH_2COOH to $CH_3CH_2CH_2COOH$

d. $CH_3CH_2COOCH_3$ to $CH_3CH_2C(CH_2CH_2CH_3)_2$
$$\begin{array}{c} | \\ OH \end{array}$$

14. What are the important industrial methods of preparing acetic anhydride?

15. Starting with carbon disulfide, show the steps in the preparation of: $CCl_2 = CCl_2$, $CHCl_3$, $CH(OC_2H_5)_3$, CCl_2F_2.

16. Outline the preparation of methylene iodide from isopropyl alcohol.

17. A substance, A, with the empirical formula $C_5H_{10}O_2$ on hydrogenation at high pressures over copper chromite as catalyst gave as products methyl alcohol and a substance B with the molecular formula $C_4H_{10}O$. The latter, when passed through a tube of aluminum oxide at elevated temperatures and then ozonized, gave acetone and formaldehyde. What is the structure of A?

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18. Indicate the reactions including the reagents and conditions for the conversions: (*a*) isobutylene to isobutane, (*b*) isopropyl alcohol to propane, (*c*) propylene dibromide to propane, (*d*) valeric acid to *n*-butane, (*e*) valeric acid to *n*-pentane.

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Chapter 9

DERIVATIVES OF AMMONIA: AMIDES, NITRILES, AMINES

A large portion of the preceding chapters has been devoted to compounds which are related to water. Thus, alcohols, ROH, may be regarded as alkyl derivatives of water; ethers, ROR, as dialkyl derivatives; acids, RCOOH, as acyl derivatives and acid anhydrides as diacyl derivatives $(RCO)_2O$. We shall now consider the corresponding nitrogen compounds which are related to ammonia. These are the amines, RNH_2, R_2NH, R_3N, and the amides, $RCONH_2$. In these substances, one or more hydrogen atoms of ammonia have been replaced by alkyl or acyl groups. We shall find the differences between water and ammonia reflected in these compounds; the derivatives of water are more acidic, those of ammonia more basic.

AMIDES

Preparation of Amides. Of the acyl derivatives of ammonia only those containing one acyl group are of importance. They are known as the amides, $RCONH_2$. The best known is **acetamide,** $CH_3\overset{\overset{\displaystyle O}{\|}}{C}-NH_2$. The following equations represent the typical methods of preparing amides as applied to acetamide.

$$CH_3COCl + 2NH_3 \longrightarrow CH_3CONH_2 + NH_4Cl$$

$$(CH_3CO)_2O + 2NH_3 \longrightarrow CH_3CONH_2 + CH_3COONH_4$$

$$CH_3COOC_2H_5 + NH_3 \longrightarrow CH_3CONH_2 + C_2H_5OH$$

The first two reactions usually take place rapidly; the reaction of esters with ammonia is slow. The parallelism between the action of ammonia (ammonolysis) and water (hydrolysis) is striking. If we substitute water for ammonia in these reactions, an acid is formed.

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Amides from Ammonium Salts. Another convenient method of preparing amides is to heat the ammonium salt of the corresponding acid.

$$CH_3COONH_4 \overset{100°-200°}{\rightleftharpoons} CH_3CONH_2 + H_2O$$

This reaction is reversible; it proceeds at an appreciable rate only at about 100° or higher. If we can remove the water as rapidly as it is formed, the reaction will go to completion in spite of an unfavorable equilibrium. Since the amides are high-boiling and the ammonium salts essentially nonvolatile substances, this is easy to accomplish by using a suitable apparatus.

Hydrolysis of Amides. The amides are hydrolyzed by boiling a water solution with acid or alkali which catalyzes the reaction. If we add one equivalent of sodium hydroxide, the reaction goes to completion for the same reason that the saponification of esters with alkali is complete (p. 97). With 1 mole of acid the reaction also goes to an end, since the ammonia is removed as the ammonium salt.

The equations for the reactions are given below:

$$RCONH_2 + NaOH \xrightarrow{\text{Boil}} RCOONa + NH_3$$

$$RCONH_2 + H_2O + H_2SO_4 \xrightarrow{\text{Boil}} RCOOH + NH_4HSO_4$$

Reaction with Nitrous Acid. When treated with nitrous acid, amides yield nitrogen and the corresponding acid. This reaction, like the hydrolysis of amides, may be used for preparing acids from the corresponding amides. Since nitrous acid is known only in dilute water solutions which slowly decompose, it is prepared by adding hydrochloric acid to an aqueous solution of sodium nitrite.

$$RCONH_2 + HONO \xrightarrow{NaNO_2 + HCl} RCOOH + N_2 + H_2O$$

Physical and Chemical Properties. The simple amides are very soluble in water and are surprisingly high-melting and high-boiling substances, as the following table illustrates.

Name	*Formula*	*Boiling Point*	*Melting Point*
Formamide	$HCONH_2$	193°	+2°
Acetamide	CH_3CONH_2	222°	81°
Propionamide	$CH_3CH_2CONH_2$	213°	79°
Butyramide	$CH_3CH_2CH_2CONH_2$	216°	116°

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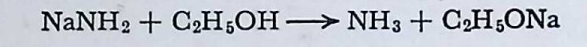
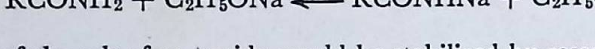
The high boiling points of the amides are probably a result of association through hydrogen bonding. The exact form of the association, however, is not clear. It does not apparently involve simple dimeric forms like the fatty acids (p. 83).

The amides may be regarded as *neutral substances*. Their acidic and basic properties are so weak that they are not manifested in water solution. This is in contrast to the parent compound, ammonia, which is a base. The substitution of an acyl group for hydrogen has greatly decreased the basic properties of the NH_2 group.

The effect of the acyl group in increasing the acidity of the $-OH$ group is apparent from a comparison of acetic acid and water (p. 77). Similarly one might expect that an amide would be a stronger *acid* than ammonia. Indeed, this is the case, but even the introduction of one acyl group has not conferred sufficient acidity on the amide, $RCONH_2$, to make it form soluble salts which are stable in water. As far as can be judged by rather approximate methods, acetamide and similar compounds are about as acidic as alcohol while ammonia is definitely a weaker acid than alcohol. Sodamide, $NaNH_2$, the sodium salt of ammonia, is decomposed by water and alcohol; the sodium derivative of acetamide only by water.



$$NaNH_2 + C_2H_5OH \longrightarrow NH_3 + C_2H_5ONa$$

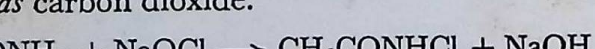


$$RCONH_2 + C_2H_5ONa \rightleftharpoons RCONHNa + C_2H_5OH$$

The anion of the salt of an amide would be stabilized by resonance to a greater degree than would the amide itself. In this the amides parallel the acids (p. 81). But, since the two contributing forms to the hybrid of the amide anion are not identical, the amount of stabilization would be less than it would in an acid anion where both contributing forms are identical.

We shall see in later chapters that when *two* acyl groups are substituted for the hydrogen atoms of ammonia (p. 229), the resulting compound is distinctly more acidic. The amides of the strong sulfonic acids (p. 427) are acidic enough to form sodium salts which are only slightly hydrolyzed by water.

The Hofmann Reaction. The most important reaction of amides is known as the *Hofmann*[1] *reaction:* the amide is converted into an alkyl derivative of ammonia, an amine, RNH_2. The mechanism of this extraordinary change is complicated. The first step consists in the replacement of a hydrogen atom by a halogen atom; the resulting compound is rapidly decomposed by alkali with the *elimination of a carbon atom as* carbon dioxide.



$$CH_3CONH_2 + NaOCl \longrightarrow CH_3CONHCl + NaOH$$

$$CH_3CONHCl + 3NaOH \longrightarrow CH_3NH_2 + NaCl + Na_2CO_3 + H_2O$$

[1] August Wilhelm von Hofmann (1818–1892), for twenty years professor at the Royal College of Chemistry, London. From 1865 until his death, professor at the University of Berlin.

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The reaction is carried out by treating an aqueous solution of the amide with sodium hypochlorite, or sodium hypobromite, and sodium hydroxide. On distilling the mixture, the amine, which is volatile, distills and is collected.

It is evident that the Hofmann reaction amounts to clipping one carbon atom from the end of a carbon chain. For this reason, it has been of importance in preparing simpler compounds from more complicated ones and in determining the structure of compounds with long carbon chains.

With the higher members of the fatty acid series the reaction proceeds a little farther and an amide RCH_2CONH_2, instead of giving a primary amine, RCH_2NH_2, yields the corresponding nitrile RCN. However, from the nitrile we can readily prepare the acid by hydrolysis (p. 87) or the amine by reduction (p. 184).

Interconversion of Amides and Nitriles. A nitrile on hydrolysis yields an acid (p. 87). The first step in this process is an amide, and the process may be used for the preparation of amides if the hydrolysis is effected by hydrogen peroxide and aqueous alkali.

$$RCN + H_2O \xrightarrow[NaOH]{H_2O_2} RCONH_2$$

The reverse of this reaction is accomplished when amides are heated with phosphorus pentoxide. The distillate consists of the more volatile nitrile.

$$RCONH_2 + P_2O_5 \xrightarrow{\text{Distill}} RCN + \underset{\text{Metaphosphoric acid}}{2HPO_3}$$

It should be noted that while the hydration (addition of water) of nitriles to amides and the dehydration of amides to nitriles is a process which can be made to go in either direction depending on the reagents employed, it is *not a reversible reaction.* A reversible reaction (as the term is usually employed) is a reaction which, in the presence of a suitable catalyst, comes to an equilibrium point in a relatively short time. In a reversible reaction changing the concentration of reactants and products alters the composition of the equilibrium mixture; and in most reversible reactions changing the temperature shifts the equilibrium. In the interconversion of amides and nitriles, while the process may be *reversed* by employing different reagents which are transformed as part of the reaction, no equilibrium is established under the usual laboratory conditions. The hydrolysis (hydration)

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reaction *runs to completion.* To reverse this reaction it is necessary to employ some dehydrating agent such as phosphorus pentoxide which will remove the elements of water from the amide by a chemical reaction. This process also goes to completion. A comparison of the interconversion of ammonium salts and amides on the one hand (a truly reversible reaction) and amides and nitriles on the other (not a reversible reaction at usual temperatures) illustrates the significant difference between two closely related types of organic reactions.

Amidines. Just as the *hydrolysis* of a nitrile produces an amide, so the *ammonolysis* of a nitrile produces a compound known as an *amidine*, $RC(=NH)-NH_2$. This ammonolysis can be accomplished by heating a nitrile with sodamide, followed by the hydrolysis of the sodium salt of the amidine.

$$RC \equiv N + NaNH_2 \longrightarrow RC(=NH)-NHNa$$

$$RC(=NH)-NHNa + H_2O \longrightarrow RC(=NH)-NH_2 + NaOH$$

The amidines differ from the amides in being bases which form salts with mineral acids which are stable in water. Thus acetamidine hydrochloride is $CH_3C(=NH)NH_2 \cdot HCl$.

THE NITRILES

Since nitriles may be regarded as dehydration products of acyl derivatives of ammonia, they may be considered here.

Methods of Preparation. The nitriles are usually prepared by the interaction of an alkyl halide with sodium or potassium cyanide (p. 24).

$$RX + KCN \longrightarrow RCN + KX$$

This reaction is satisfactory only if the alkyl halide is derived from a primary or secondary alcohol. With highly branched compounds other inorganic cyanides, such as cuprous cyanide, are more satisfactory.

A second method of preparing nitriles starts with the corresponding aldehyde. This is converted into the oxime, which is dehydrated with acetic anhydride.

$$RCHO \xrightarrow{NH_2OH} RCH=NOH \xrightarrow{(CH_3CO)_2O} RCN$$

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The preparation of nitriles from acids through the amides has just been considered. Nitriles can also be prepared by passing an acid and ammonia over a catalyst at a high temperature.

$$RCOOH + NH_3 \xrightarrow[500^\circ]{\text{Catalyst}} RCN + 2H_2O$$

The process undoubtedly proceeds through the formation of the ammonium salt and its subsequent dehydration.

Nomenclature. The nitriles are usually named from the acid into which they are converted by hydrolysis; thus, **acetonitrile** is CH_3CN, because on hydrolysis this substance yields acetic acid, CH_3COOH. Similarly, we have **propionitrile,** CH_3CH_2CN. Another method of naming these compounds is to consider them as esters of hydrocyanic acid (HCN). Thus acetonitrile may be called *methyl cyanide*, and propionitrile, *ethyl cyanide*.

Physical and Chemical Properties. The lower nitriles are colorless liquids boiling somewhat lower than the acids into which they can be hydrolyzed. They have neither acidic nor basic properties.

PHYSICAL PROPERTIES OF THE SIMPLE NITRILES

Name	*Formula*	*Boiling Point*
Acetonitrile	CH_3CN	81.6°
Propionitrile	CH_3CH_2CN	98°
n-Butyronitrile	$CH_3CH_2CH_2CN$	118.5°
Isobutyronitrile	$(CH_3)_2CHCN$	107°

The triple linkage between carbon and nitrogen is characteristic of a nitrile. It represents an unsaturation somewhat similar to that which occurs in acetylene, and we should expect that the nitriles would combine with two or four monovalent atoms or groups. Of course, the reagents which add to a carbon-nitrogen triple bond are often quite different from those which add to a carbon-carbon triple bond. Some of the addition reactions of nitriles have already been mentioned, and these, together with some new reactions, are listed below.

1. *Hydrolysis.*

$$RCN + H_2O \longrightarrow RCONH_2$$

The amide can be further hydrolyzed to an acid.

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2. *Alcoholysis.*

$$RCN + CH_3OH + HCl \longrightarrow RC(OCH_3) = NH{\cdot}HCl$$

An imido ester hydrochloride

3. *Ammonolysis.*

$$RCN + \underset{\text{(Liquid)}}{NH_3} \xrightarrow{(NaNH_2)} \underset{\text{An amidine}}{RC(=NH)NH_2}$$

4. *Grignard Reaction.*

$$RCN + R'MgX \longrightarrow \begin{matrix} R \\ R' \end{matrix}\!\!>C = NMgX \xrightarrow{H_2O} \begin{matrix} R \\ R' \end{matrix}\!\!>C = O$$

5. *Reduction.*

$$RCN + 4[H] \longrightarrow \underset{\text{A primary amine}}{RCH_2NH_2}$$

6. *Conversion to Aldehydes.*

$$RCN + 2[H] \xrightarrow[HCl]{SnCl_2} RCH = NH \xrightarrow{\text{Hydrolysis}} RCHO + NH_3$$

Only this particular reducing agent is employed.

Since the nitrile RCN can be easily made in two steps from the alcohol ROH, these reactions give us a method of preparing a number of compounds from a given alcohol.

Isonitriles. The isonitriles are isomeric with the nitriles. In isonitriles the alkyl group is attached to nitrogen instead of carbon. Isonitriles are formed, together with nitriles, by the interaction of an alkyl halide and a metallic cyanide. If silver cyanide is used the main product is an isonitrile.

$$RI + AgCN \longrightarrow RNC + AgI$$

The isonitriles are also known as the *carbylamines* or the *alkyl isocyanides*. The lower members of the series are liquids insoluble in water and with boiling points somewhat lower than the isomeric nitriles. They have a peculiarly bad odor.

On hydrolysis the isonitriles yield a primary amine (see below) and formic acid.

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The carbon atom has the ability to combine with other atoms as illustrated by the reaction of an isocyanide with sulfur or silver oxide.

$$RNC + S \xrightarrow{120^\circ} \underset{\text{An isothiocyanate}}{RNCS}$$

$$RNC + Ag_2O \longrightarrow \underset{\text{An isocyanate}}{RNCO} + 2Ag$$

The structure of the isonitrile group is considered later in this chapter (p. 194).

AMINES

Nomenclature. The amines are the alkyl derivatives of ammonia. They may be divided into the following classes:

1. A primary amine, RNH_2, e.g., CH_3NH_2 methylamine,
2. A secondary amine, R_2NH, e.g., $(CH_3)_2NH$ dimethylamine,
3. A tertiary amine, R_3N, e.g., $(CH_3)_3N$ trimethylamine.

The usual method of naming amines is illustrated by the above examples. In more complicated amines, the position of the group may be indicated and the name of the parent hydrocarbon given. Thus, $(CH_3)_2CHCHNH_2CH_3$ is 2-amino-3-methylbutane. It should be noted that the group NH_2 is called *ami***no** when present in an *amine* and *ami***do** when present in an *amide*.

General Properties of Amines. The simpler amines resemble ammonia. They are soluble in water and the solutions are basic. On boiling the solution the volatile amines are expelled. The boiling points of some of the simpler amines are given below.

BOILING POINTS OF SIMPLE AMINES

Name	*Formula*	*Boiling Point*	*Class*
Methylamine	CH_3NH_2	-7°	Primary amine
Dimethylamine	$(CH_3)_2NH$	$+7^\circ$	Secondary amine
Trimethylamine	$(CH_3)_3N$	$+4^\circ$	Tertiary amine
Ethylamine	$C_2H_5NH_2$	$+17^\circ$	Primary amine
n-Propylamine	$CH_3CH_2CH_2NH_2$	$+49^\circ$	Primary amine

Neutralization of Amines. All three classes of amines are bases like ammonia. The water solutions turn red litmus blue and may be neutralized with acids. The salts which are thus formed are obtained as white solids by evaporating the solution. Like inorganic salts they are nonvolatile solids, readily soluble in water and insoluble in organic solvents. Their water solutions are ionized. All these facts are

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best represented by the following ionic equations, using trimethylamine as the example.

$$(CH_3)_3N + H_2O \rightleftharpoons (CH_3)_3NH^+ + OH^-$$
$$(CH_3)_3NH^+ + OH^- + H^+ + Cl^- \longrightarrow (CH_3)_3NH^+ + Cl^- + H_2O$$

Similar equations may be written for the primary and secondary amines. The chlorides may also be formed by bringing together the base and acid in an anhydrous medium.

$$(CH_3)_3N + HCl \longrightarrow (CH_3)_3NHCl$$

In electronic formulation this reaction becomes

$$CH_3 : \underset{\underset{\cdot\cdot}{CH_3}}{\overset{\overset{\cdot\cdot}{CH_3}}{\ddot{N}}} : + H : Cl \longrightarrow \left[CH_3 : \underset{\underset{\cdot\cdot}{CH_3}}{\overset{\overset{\cdot\cdot}{CH_3}}{\ddot{N}}} : H \right]^+ Cl^-$$ (See p. 192.)

The salts of the amines are alkyl derivatives of the ammonium salts and are usually named on this basis, thus: CH_3NH_3Cl, methylammonium chloride; $(CH_3)_2NH_2Br$, dimethylammonium bromide; $(CH_3)_3NHNO_3$, trimethylammonium nitrate. The formulas of the salts are also written to show more clearly the original amine and are named as hydrochlorides, thus:

$CH_3NH_2{\cdot}HCl$ Methlyamine hydrochloride

This method corresponds to an obsolete method of writing ammonium salts, thus: $NH_3{\cdot}HCl$, the hydrochloride of ammonia.

Like ammonia, the amines form double salts with platinum chloride and gold chloride; for example, $(CH_3NH_3)_2PtCl_6$ and $CH_3NH_3AuCl_4$. These salts are usually sparingly soluble in water, and are frequently used in isolating and identifying the amines. Their melting points are often characteristic, and a determination of the percentage of metal in the compound enables one to calculate the molecular weight of the amine.

Preparation of Amines from Their Salts. On treating a solution of the salt of an amine with sodium hydroxide, the free amine is formed in the solution. If the solution is then boiled, the amine will be expelled, if volatile; if the solution is extracted with ether, the amine will pass into the ether layer.

$$(CH_3)_3NHCl + NaOH \longrightarrow (CH_3)_3NHOH + NaCl$$
$$(CH_3)_3NHOH \underset{\text{Distill or extract}}{\rightleftharpoons} (CH_3)_3N + H_2O$$

This behavior of the salts of the amines is exactly parallel to the reaction of ammonium salts. It shows that the amines like ammonia are

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weak anhydro bases. Thus, to obtain weak bases from their salts, we treat a solution of the salt with a strong base, and boil or extract; if the weak base is insoluble (as are the higher amines), it will precipitate. This general method should be compared with the preparation of weak acids from their salts by the action of a strong nonvolatile acid (p. 75).

Basic Dissociation Constants. The relative strength of weak bases may be best expressed in terms of a basic dissociation constant. This is similar to the acid dissociation constant which we have already mentioned (p. 77). All the weak organic bases belong to the class of substances which are called *anhydro bases*. A water solution of such a base contains the anhydro base itself (e.g., RNH_2), any undissociated hydrated base (RNH_3OH) and the dissociated base ($RNH_3^+ + OH^-$). In measuring the strength of an anhydro base we lump together both the unhydrated base, RNH_2, and the undissociated base, RNH_3OH, and call this total the *free base*. A measure of the strength of the base is thus the amount of dissociated base ($RNH_3^+ + OH^-$) compared to the total free base ($RNH_3OH + RNH_2$). Therefore, we write:

$$\text{Basic Dissociation Constant } (K_B) = \text{Conc. } OH^- \times \left(\frac{\text{conc. of ion } (RNH_3^+)}{\text{conc. free base}}\right)$$

A solution containing equal molecular amounts of a weak anhydro base and its salt has a concentration of hydroxyl ion equal to the basic dissociation constant. The constant, K_B, for ammonia is 2×10^{-5} and the hydroxyl ion concentration of an ammonium hydroxide—ammonium chloride mixture is about 10^{-5}, since conc. $H^+ \times$ conc. $OH^- = 10^{-14}$, the conc. of hydrogen ion in this solution is about 10^{-9}.

The basic dissociation constants for some of the common amines are as follows:

Methylamine	$K_B = 5 \times 10^{-4}$
Dimethylamine	$K_B = 5.4 \times 10^{-4}$
Trimethylamine	$K_B = 5.9 \times 10^{-5}$

It is evident that they are somewhat stronger bases than ammonia itself. The relative strengths of certain bases are shown in the diagram in Fig. 9.

Preparation of Primary Amines. Special methods are employed for preparing a number of the different amines; we shall consider only the general methods of preparing primary amines. These are as follows:

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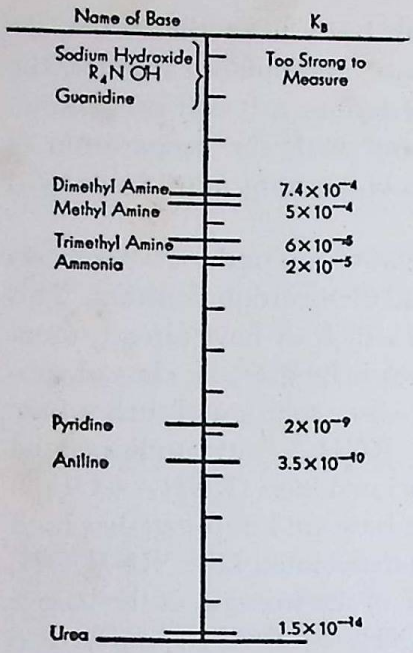

FIG. 9. The relative strengths of certain bases. The strongest bases are at the top of the scale; each scale unit corresponds to a ten-fold change in the basic dissociation constant.

1. *Reduction of a Nitrile* (p. 184).
2. *Hofmann Reaction* (p. 180).
3. *Phthalimide Synthesis.* (This will be discussed when phthalimide is considered in Chap. 26.)
4. *Reduction of Oximes.*

$$R_2C = NOH + 4[H] \longrightarrow R_2CHNH_2 + H_2O$$

5. *Reduction of Nitro Compounds.*

$$CH_3NO_2 + 6[H] \longrightarrow CH_3NH_2 + 2H_2O$$

This last method has been of little importance for the preparation of the type of amine we are here considering, but is of great importance in aromatic chemistry where the nitro compounds are easily obtained. With the simple aliphatic nitro compounds becoming available (p. 43) their importance as a source of primary amines may increase.

Preparation of Amines from Ammonia. On heating ammonia with an alkyl halide, the two combine to form the salt of a primary amine. Unfortunately the reaction does not stop here, but forms secondary and tertiary amines and also substances known as *quaternary ammonium salts.* This unpromising mixture can be separated, and a number of amines have been prepared by this method. Since, however, so many products are formed, the process is not efficient for the preparation of any one amine.

$$C_2H_5Br + NH_3 \longrightarrow C_2H_5NH_3Br$$
$$C_2H_5NH_3Br + NH_3 \rightleftharpoons C_2H_5NH_2 + NH_4Br$$

$$C_2H_5NH_2 + C_2H_5Br \longrightarrow (C_2H_5)_2NH_2Br$$
$$(C_2H_5)_2NH_2Br + NH_3 \rightleftharpoons (C_2H_5)_2NH + NH_4Br$$

$$(C_2H_5)_2NH + C_2H_5Br \longrightarrow (C_2H_5)_3NHBr$$
$$(C_2H_5)_3NHBr + NH_3 \rightleftharpoons (C_2H_5)_3N + NH_4Br$$

$$(C_2H_5)_3N + C_2H_5Br \longrightarrow (C_2H_5)_4NBr$$

Tetraethylammonium bromide (a quaternary ammonium salt)

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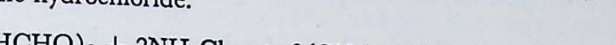
Preparation of Methyl Amines from Formaldehyde. By heating formaldehyde solution with a large excess of ammonium chloride, methylamine hydrochloride is formed.



$$2HCHO + NH_4Cl \longrightarrow CH_3NH_2{\cdot}HCl + HCOOH$$

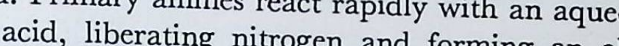
The amine hydrochloride is separated from the excess ammonium chloride by virtue of the fact that it is soluble in absolute alcohol while ammonium chloride is not.

When trioxane and ammonium chloride are mixed and heated together for some time, the mass liquefies and carbon dioxide is liberated. The product is largely trimethylamine hydrochloride.

$$3(HCHO)_3 + 2NH_4Cl \longrightarrow 2(CH_3)_3N{\cdot}HCl + 3CO_2 + 3H_2O$$

Since the initial materials are so cheap, methylamine and trimethylamine are prepared by these reactions.

Reactions of Amines with Nitrous Acid. Primary, secondary, and tertiary amines can be distinguished by their behavior toward nitrous acid. Primary amines react rapidly with an aqueous solution of nitrous acid, liberating nitrogen and forming an alcohol. The reaction may be illustrated with methylamine and nitrous acid.

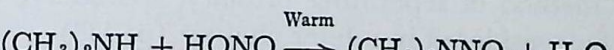


$$CH_3NH_2 + HONO \longrightarrow CH_3OH + N_2 + H_2O$$

The reaction between nitrous acid and a primary amine with more than two carbon atoms in the molecule does not lead exclusively to the alcohol formed by replacement of $-NH_2$ by $-OH$. Instead this normal product is almost always accompanied by isomeric alcohols. Propylamine and nitrous acid, for example, furnish a mixture of *n*-propyl and isopropyl alcohols.

$$CH_3CH_2CH_2NH_2 + HNO_2 \begin{cases} \nearrow CH_3CH_2CH_2OH \\ \searrow CH_3CHOHCH_3 \end{cases}$$

Secondary amines react slowly with nitrous acid forming **nitroso compounds** which often separate from the solution as oils.



$$(CH_3)_2NH + HONO \xrightarrow{\text{Warm}} \underset{\text{Nitroso dimethyl amine}}{(CH_3)_2NNO} + H_2O$$

Tertiary amines form the corresponding salt (a tertiary amine nitrite) when treated with nitrous acid, but undergo no further change; the amine may be recovered from the nitrite in the usual manner by adding alkali.

Acylation of Amines. The primary and secondary amines (but not the tertiary) can be acylated by interaction with an acid chloride or an acid anhydride. The products are alkylated amides; on hydroly-

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sis, the original amine is regenerated. The following equations illustrate these reactions.

$$2CH_3NH_2 + CH_3COCl \longrightarrow \underset{\text{Methylacetamide}}{CH_3CONHCH_3} + CH_3NH_3Cl$$

$$2(CH_3)_2NH + CH_3COCl \longrightarrow \underset{\text{Dimethylacetamide}}{CH_3CON(CH_3)_2} + (CH_3)_2NH_2Cl$$

$$2RNH_2 + (R'CO)_2O \longrightarrow R'CONHR + R'COONH_3R$$

$$2R_2NH + (R'CO)_2O \longrightarrow R'CONR_2 + R'COONH_2R_2$$

Tests for Amines and Amides. Amides are distinguished from amines by their inability to form salts with acids in water solution, and by the formation of ammonia on alkaline hydrolysis. The amines cannot be hydrolyzed with either acids or bases. Both amides and *primary* amines liberate nitrogen when treated with nitrous acid but the products are different; the former yields an acid, the latter an alcohol.

There are a number of tests to enable one to distinguish between a primary, a secondary, and a tertiary amine. The difference in behavior with nitrous acid is often used; if nitrogen is evolved a primary amine is present (it having been first proved that the compound is not an amide). Another characteristic reaction of primary amines is the peculiarly offensive odor produced when they are warmed with chloroform and potassium hydroxide. This is due to the formation of an isonitrile (p. 184).

$$RNH_2 + CHCl_3 + 3KOH \longrightarrow \underset{\text{Isonitrile}}{RNC} + 3KCl + 3H_2O$$

Secondary and tertiary amines may be distinguished the one from the other by (1) the nitrous acid reaction mentioned above (p. 189), and (2) the fact that secondary amines but not tertiary amines may be acylated. A method of separating primary, secondary, and tertiary amines will be considered in a later chapter (p. 428).

QUATERNARY AMMONIUM COMPOUNDS

We have seen that (p. 188) when a tertiary amine is heated with an alkyl halide the two combine, forming a substance known as a *quaternary ammonium salt.*

$$R_3N + RX \longrightarrow R_4NX$$

For example, trimethylamine, $(CH_3)_3N$, when heated with methyl

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iodide yields tetramethylammonium iodide, a quaternary ammonium salt.

Physical and Chemical Properties. Quaternary ammonium salts resemble the salts of amines in their physical properties, being crystalline solids soluble in water. They differ very markedly, however, in their chemical behavior. The salts of the amines when treated with a strong base like sodium hydroxide are decomposed forming the free amine. The quaternary ammonium salts do not react with sodium hydroxide in aqueous solution. The reason for this becomes evident when one examines the product of the reaction of silver hydroxide on a quaternary ammonium iodide. In this case a reaction does take place because silver iodide is insoluble in water.

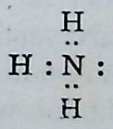
$$(CH_3)_4NI + AgOH \longrightarrow (CH_3)_4NOH + \underset{\text{Insoluble}}{AgI}$$

If the silver iodide is filtered, the resulting aqueous solution is found to be *strongly alkaline;* on evaporation at low temperature a crystalline solid is obtained which has the composition corresponding to $(CH_3)_4NOH{\cdot}5H_2O$. This substance (which is very deliquescent) is a strong base comparable with potassium or sodium hydroxide. It will absorb carbon dioxide from the air, forming a carbonate. An examination of the properties of the aqueous solution of this strong base shows that it is a solution of the hydroxyl ion and the quaternary ammonium ion, $(CH_3)_4N^+$. When neutralized with an acid, the quaternary ammonium base forms the corresponding salt. In this way the iodide may be regenerated by neutralizing the solution with hydrogen iodide.

$$(CH_3)_4NOH + HI \longrightarrow (CH_3)_4NI + H_2O$$

Quaternary ammonium salts containing one large alkyl group (e.g., dimethyl-ethyl-octadecyl-ammonium bromide) are detergents and effective bactericides. They will be mentioned again in the discussion of soap and detergents on page 213.

Electronic Formulas for Nitrogen Compounds. The nitrogen atom has five valence electrons and the maximum number that can be in the outer shell is eight. In ammonia three of these are used in pairing with the electrons of three separate hydrogen atoms. This leaves in ammonia an *unshared pair of electrons.*



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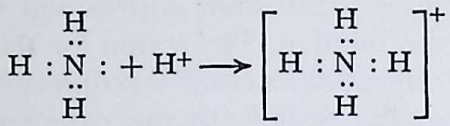
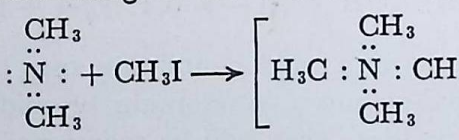
The basic properties of ammonia are due to this unshared pair which can attract and hold a hydrogen ion (often called a *proton*). The resulting product has a positive charge and is an ion because the total number of valence electrons is *one less* than the number belonging to each of the component atoms (8 as compared with 3 + 1 + 5). The essential reaction which is involved in the neutralization of ammonia by hydrochloric acid may be represented as follows.



In a similar way, in trimethylamine three of the five electrons of the nitrogen atom are involved in forming pairs with three electrons from three different methyl groups. Here again an unshared pair of electrons is left on the nitrogen atom and, like ammonia, trimethylamine is a base.

The unshared pair of electrons in trimethylamine cannot only combine with a proton, but it can also combine with another methyl group. This occurs slowly when the compound is heated with methyl iodide and the resulting product is the quaternary salt, tetramethylammonium iodide. All the nitrogen valence electrons are used in forming electron pairs. In this process the iodine atom has gained one electron, making a total of eight, and thus acquired a negative charge (since it has one more electron than in the neutral atom). The electron which the iodine atom has gained has been lost from the nitrogen, thus giving a positive charge of one unit to the whole ion.



Of the eight electrons surrounding the nitrogen atom in the positive ion, four may be regarded as being contributed by the four carbon atoms and four from the nitrogen. This latter number is one less than the number of electrons associated with this normal nitrogen atom, and it is the loss of this electron which gives the positive charge to the ion.

We are now ready to consider the distinction between the tetramethylammonium ion $(CH_3)_4N^+$ and the trimethylammoniun ion $(CH_3)_3NH^+$. The latter is the substance which is formed by the addition of a proton to trimethylamine when the amine is neutralized

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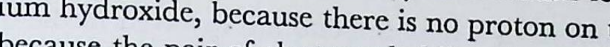
with an acid. The gain and loss of a proton from a nitrogen atom is a process which is instantaneous and reversible. Therefore, when we treat the trimethylammonium ion with a strong base, that is with a high concentration of hydroxyl ions, the hydroxyl ion takes away the proton forming water.

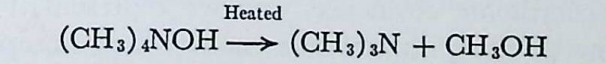


$$(CH_3)_3NH^+ + OH^- \longrightarrow (CH_3)_3N + H_2O$$

This cannot happen when the tetramethylammonium ion is treated with potassium hydroxide, because there is no proton on the nitrogen atom, and because the pair of electrons holding the methyl group to nitrogen does not break under these circumstances.

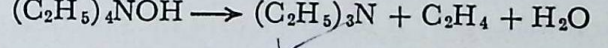
Another explanation of the striking difference in basicity between amines and quaternary ammonium hydroxides is based on hydrogen bonding. There is evidence that in an aqueous solution of an amine a considerable portion of the amine is in the hydrated form, which may be regarded as the undissociated base. The reason for the stability of an undissociated base such as $(CH_3)_3NHOH$ is thought to be the hydrogen bond by which the hydroxyl group is joined to the balance of the molecule. There being no hydrogen on nitrogen in a quaternary ammonium hydroxide, there can be no hydrogen bond to hold together the undissociated base.

Decomposition of Quaternary Bases on Heating. Although the pair of electrons holding the methyl group to nitrogen is not broken in aqueous solution, it can be broken if the molecule is heated. Thus tetramethylammonium hydroxide decomposes on heating to give trimethylamine and methyl alcohol. The hydroxyl ion combines with a methyl group and forms methyl alcohol.



$$(CH_3)_4NOH \xrightarrow{\text{Heated}} (CH_3)_3N + CH_3OH$$

The quaternary ammonium bases which have higher alkyl groups decompose somewhat differently. Heating results in the formation of a molecule of water, an unsaturated compound, and a tertiary amine.



$$(C_2H_5)_4NOH \longrightarrow (C_2H_5)_3N + C_2H_4 + H_2O$$

This decomposition of quaternary ammonium bases is sometimes useful in determining the structure of complex amines (p. 605) as it gives a method of eliminating the more complex group from the molecule in the form of an unsaturated hydrocarbon.

The Amine Oxides. When a tertiary amine is treated with hydrogen peroxide a very interesting substance known as an *amine oxide* is

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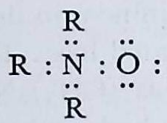
formed:

$$(CH_3)_3N + H_2O_2 \longrightarrow (CH_3)_3NO + H_2O$$

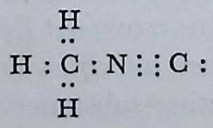
The amine oxides crystallize as hydrates, for example $(CH_3)_3NO{\cdot}2H_2O$ (mp 98°). If we regard the nitrogen atom as having a valence of five, we would be inclined to write the structure of an amine oxide as $(CH_3)_3N = O$. The electronic formula equivalent to this would contain a nitrogen atom having ten electrons in the outer shell, $:\ddot{\underset{\cdot\cdot}{N}}::\ddot{\underset{\cdot\cdot}{O}}$. All four electrons of a double bond are involved in the outer shell of each of the two connected atoms. Now a variety of considerations have convinced physicists that nitrogen cannot have more than eight valence electrons in the outer shell. This excludes the formula which contains a double linkage; in place of this we must write the following formula.



In this formula both the nitrogen and the oxygen atoms have octets. However, the covalent bond between nitrogen and oxygen has not been formed by the sharing of two electrons, one contributed by each of the two atoms joined by the bond. Instead both electrons have been furnished by a single atom, the nitrogen atom. To the extent that the nitrogen atom does share this pair of electrons with the oxygen atom, the nitrogen atom becomes relatively positive and the oxygen atom relatively negative. The resulting polarity is less than that corresponding to the charge on a monovalent ion. We call a covalent bond of this kind a coordinate covalence, and we represent it by a singly barbed arrow pointing toward the atom which accepts electrons, thus $(CH_3)_3N{\rightharpoonup}O$. The considerable polarity in the amine oxides is reflected in their large dipole moments (p. 71). The moment of trimethylamine oxide is 5.0×10^{-18} electrostatic units.

The "formal charge" written in parentheses in one resonating form of the simple acids (p. 81) is identical with the coordinate covalence.

Structure of Isonitriles. The isonitriles (p. 184) are somewhat similar in their structure to the amine oxides. The electronic formula for methyl isocyanide, CH_3NC, is



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In this formula there are only three "bonds" joining the nitrogen and carbon (three pairs of electrons or a total of six), but the nitrogen atom has one less electron than it usually carries and the carbon one more; therefore there is a difference in charge inside the molecule as in the amine oxides. This may be represented by the formula $RN \equiv C$.

Basic Properties of Oxygen and of Sulfur. If we write the electronic formula of dimethyl ether it is evident that the oxygen atom contains two unshared pairs of electrons.

$$H_3C : \ddot{\underset{\cdot\cdot}{O}} : CH_3$$

It might be expected that one or both of these pairs could add a proton just as the unshared pair in trimethylamine adds a proton. We might thus predict that ethers would have basic properties. As a matter of fact, they do, but the tendency of the proton to stay attached to oxygen is very much less than the tendency of the proton to stay attached to nitrogen. The salts of an ether are therefore decomposed in water solution; if we treat an ether with concentrated hydrochloric acid, however, the ether dissolves in large quantities. A salt is formed of which the positive ion probably has the formula

$$\left[R : \overset{H}{\underset{\cdot\cdot}{\ddot{O}}} : R \right]^+$$

In certain cyclic compounds containing oxygen, the basic properties of oxygen are very pronounced, and the salts of these compounds are stable in water solution. A consideration of these compounds will be postponed, however, until Chap. 31.

Like oxygen, the normal sulfur atom contains six valence electrons, and the sulfur analog of an ether $R : \ddot{\underset{\cdot\cdot}{S}} : R$ might be expected to have basic properties. The attraction for a proton is very weak, however, and like the oxygen compound, the substances show no basic properties in aqueous solution.

Amines and Quaternary Bases of Biochemical Interest. Methylamine, dimethylamine, and trimethylamine are found in small quantities in nature. They are formed during bacterial decomposition of the proteins and other complex nitrogenous compounds. Trimethylamine occurs in herring brine and in the residues from the manufacture of beet sugar.

Two **diamines** (i.e., compounds with two amino groups) are formed in considerable quantities when proteins putrefy. They are **putrescine**

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(tetramethylenediamine), $NH_2CH_2CH_2CH_2CH_2NH_2$ (bp 158°), and **cadaverine** (pentamethylenediamine), $NH_2CH_2(CH_2)_3CH_2NH_2$ (bp 178°). They both have a disagreeable odor and are poisonous. A tetramine, **spermine,** has been isolated from human sperm and its structure established as $NH_2(CH_2)_3NH(CH_2)_4NH(CH_2)_3NH_2$. It will be noted that it may be regarded as putrescine with the group $NH_2CH_2CH_2CH_2$ substituted on a nitrogen at each end of the chain.

Choline. A quaternary ammonium base, β-hydroxyethyl-trimethylammonium hydroxide, $HOCH_2CH_2N(CH_3)_3OH$ occurs widely distributed in nature, usually combined with an organic ester of phosphoric acid. Lecithin, whose structure will be considered in the next chapter, is an example of such a compound. In the body choline is set free from the lecithin of the foodstuffs and its presence seems to be essential to the proper utilization of fats by the animal body.

Acetyl Choline, $CH_3COOCH_2CH_2N(CH_3)_3OH$, is a substance with a very powerful physiological action (100,000 times more powerful than choline itself). When injected into the blood stream it causes a fall of the blood pressure. It has a powerful contractile effect on muscle tissue even in minute quantities. In certain cases, the animal body appears to utilize this action of acetyl choline in transmitting a nerve impulse to a muscle. Acetyl choline is liberated at the nerve endings when the nerve is stimulated.

QUESTIONS AND PROBLEMS

1. Define and illustrate the following terms: *coordinate covalence, ammonolysis, isonitrile, quaternary ammonium salt, amidine.*

2. Write balanced equations for the preparation of propionamide from the acid, the acid chloride, the acid anhydride, and from ethyl propionate.

3. Write structural formulas for: isobutyramide, methyl-diethyl-amine, ethyl acetamide, dibutylamine, trimethylpropylammonium chloride.

4. Acetamide can be dehydrated to acetonitrile, and the nitrile can be hydrated to the amide. Why are these interconversions not considered to be an equilibrium process?

5. Write equations for the reaction of nitrous acid and (*a*) trimethylamine, (*b*) butyramide, (*c*) propylamine, (*d*) diethylamine.

6. How would you go about the preparation of (*a*) ethylamine from its hydrochloride, and (*b*) octylamine from its hydrochloride?

7. Indicate the steps in the preparation of $(C_2H_5)_2CHNH_2$ from propionic acid.

8. Write equations for the reaction between propionitrile and (*a*) $H_2O_2 + NaOH$, (*b*) $SnCl_2 + HCl$, (*c*) CH_3MgI, (*d*) $H_2 + Ni$, (*e*) NH_3.

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9. Describe methods for preparing methylamine and trimethylamine.

10. Write electronic structures for triethylammonium bromide and tetraethylammonium bromide. Explain the difference in basicity between the two bases.

11. An unknown substance is either hexylamine, or ethylbutylamine or dimethylbutylamine. What chemical tests would you use to distinguish between these possibilities?

12. Write balanced equations for the reactions between propionamide and (*a*) $Br_2 + NaOH$, (*b*) $H_2O + NaOH$, (*c*) $NaNO_2 + HCl$, (*d*) P_2O_5.

13. An amine has the molecular formula $C_4H_{11}N$. Write the possible structural formulas for the amine. On treatment with chloroform and alkali the amine forms an isonitrile, detectable by its odor. What structural formulas are eliminated by this reaction? What reactions would you use to distinguish between the remaining structures?

14. Write electronic formulas for triethylamine oxide and for ethyl isocyanide.

15. What products would you expect to obtain from (*a*) $CH_3CH_2CH_2COCl$ and CH_3NH_2, (*b*) $(CH_3CH_2CH_2)_4NOH$ on heating, (*c*) $(CH_3)_2CHCOCl$ and $(CH_3)_2NH$?

16. When absolute ether is shaken with a large excess of cold concentrated sulfuric acid, a reaction occurs and a disappearance of the ether layer is noticed. Explain what happens. How may most of the ether be recovered?

17. The following pairs of compounds are allowed to interact: (*a*) methyl-ethyl-propyl amine and methyl iodide, (*b*) dimethyl-propyl-amine and ethyl iodide, (*c*) dimethyl-ethyl-amine and *n*-propyl iodide. Are these three products identical or different? Explain. What is the significance of these results?

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Chapter 10

POLYHYDRIC ALCOHOLS: FATS AND OILS

In previous chapters we have seen that many classes of organic compounds are characterized by having a certain reactive group in the molecule. Such reactive groups as the hydroxyl group of alcohols, the carboxyl group of acids, and the carbonyl group of aldehydes and ketones are known as *functional groups*. Up to this point we have considered only compounds which have one such functional group. Many important organic compounds, however, contain several functional groups and are known as *polyfunctional compounds*. We begin their study in this chapter. This study is simplified by the fact that, usually, each functional group reacts exactly as it would if it occurred alone. Thus the reactions of complicated substances may be predicted in many instances from a knowledge of simple compounds. Exceptions to this rule will be noted.

As an introduction to the study of polyfunctional compounds we shall consider those substances which contain several hydroxyl groups in the molecule. These are known as the *polyhydric alcohols*. Two compounds of this class, ethylene glycol, $C_2H_4(OH)_2$, and glycerine (glycerol), $C_3H_5(OH)_3$, are of great importance; the first because of its cheap commercial production from ethylene, and the other because it is the alcohol which is combined with complex organic acids in animal fats and vegetable oils.

The simplest polyhydric alcohols are the **glycols;** these are compounds having the general formula $C_nH_{2n}(OH)_2$. They are derivatives of the saturated hydrocarbons in which two hydrogens have been replaced by hydroxyl groups. Compounds containing two hydroxyl groups on the *same* carbon atom, e.g., $RCH(OH)_2$, are not included in this class. We have previously noted (p. 141) that attempts to prepare such a compound usually fail because of the elimination of water and the formation of an aldehyde or ketone. Therefore, the first member of the glycol series is **ethylene glycol,** CH_2OHCH_2OH, which has two hydroxyl groups on adjacent carbon atoms.

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GLYCOLS

Preparation of Ethylene Glycol. Just as an alcohol may be prepared from an alkyl halide, so a glycol may be prepared from the corresponding dihalide. Thus by the action of silver hydroxide on ethylene dibromide, ethylene glycol is formed.

$$CH_2BrCH_2Br + 2AgOH \longrightarrow CH_2OHCH_2OH + 2AgBr$$

Ethylene glycol is prepared commercially from ethylene by two different processes. In one, hypochlorous acid is added to ethylene and the product, **ethylene chlorohydrin** (p. 57), is heated with sodium bicarbonate solution at 70° to 80° for 4 to 6 hours. Under these conditions the chlorine atom is replaced by a hydroxyl group.

$$\underset{\text{Ethylene chlorohydrin}}{CH_2ClCH_2OH} + NaHCO_3 \longrightarrow CH_2OHCH_2OH + NaCl + CO_2$$

In the other, ethylene is oxidized to ethylene oxide (p. 62) and the oxide is heated with water in the presence of a small amount of acid as a catalyst.

$$\underset{\diagdown\ O\ \diagup}{CH_2 - CH_2} + HOH \xrightarrow{\text{Acid}} CH_2OHCH_2OH$$

The direct transformation of ethylene to ethylene glycol can be effected by treatment with potassium permanganate (p. 60) or hydrogen peroxide (p. 203).

Properties and Uses of Ethylene Glycol. Ethylene glycol is a slightly sweet, mobile liquid, miscible with water in all proportions, but only slightly miscible with ether. It boils at 197° and solidifies at −11.5°. Ethylene glycol has been used extensively as a solvent and as a substance to be added to the water in the radiators of automobiles to prevent freezing under winter conditions. It is also used in the preparation of certain resins (p. 229).

Chemical Properties of Ethylene Glycol. The chemical reactions of ethylene glycol correspond to the fact that it has two primary hydroxyl groups. For example, it may be oxidized to the corresponding acid, oxalic acid, which contains two carboxyl groups.

$$\begin{matrix} CH_2OH \\ | \\ CH_2OH \end{matrix} + 4[O] \longrightarrow \underset{\text{Oxalic acid}}{\begin{matrix} COOH \\ | \\ COOH \end{matrix}} + 2H_2O$$

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When treated with concentrated hydrochloric acid or hydrobromic acid, ethylene dichloride or dibromide is formed. By controlling the concentration of the acid and the temperature, the reaction may be stopped at the first product, ethylene chlorohydrin or bromohydrin.

$$\begin{array}{c} CH_2OH \\ | \\ CH_2OH \end{array} \xrightarrow{HBr} \begin{array}{c} CH_2Br \\ | \\ CH_2OH \\ \text{Ethylene} \\ \text{bromohydrin} \end{array} \xrightarrow{HBr} \begin{array}{c} CH_2Br \\ | \\ CH_2Br \end{array}$$

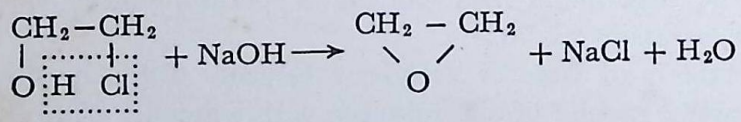
Ethylene glycol is dehydrogenated by lead tetracetate or periodic acid, the C–C bond being ruptured to form two molecules of formaldehyde.

$$CH_2OHCH_2OH + Pb(OCOCH_3)_4 \longrightarrow 2HCHO + 2CH_3COOH + Pb(OCOCH_3)_2$$

$$CH_2OHCH_2OH + HIO_4 \longrightarrow 2HCHO + HIO_3 + H_2O$$

This oxidative cleavage is general for 1,2-diols. It is of value both because it makes possible the preparation of a number of aldehydes and ketones which would otherwise be difficult to obtain, and because it enables us to break a carbon chain at a particular place. The cleavage may be considered to be the reversal of the dimolecular reduction of ketones to pinacols discussed on p. 135.

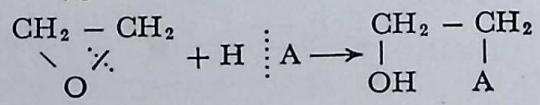
Ethylene Oxide. When ethylene chlorohydrin is heated with a solution of sodium hydroxide, hydrogen chloride splits out and a cyclic ether known as *ethylene oxide* is formed.



The direct synthesis of ethylene oxide from ethylene and oxygen has already been noted on p. 62.

Ethylene oxide is soluble in water and boils at 13°. Mixed with 9 parts of carbon dioxide, it forms an important fumigant for foodstuffs and books because of the ease with which it can be removed by exposure to air.

Ethylene oxide, unlike diethyl ether, is very reactive. In most of its reactions the oxido ring behaves like a carbonyl group: reagents, which may be formulated as HA, add to ethylene oxide opening the ring, H going to oxygen and A going to carbon.



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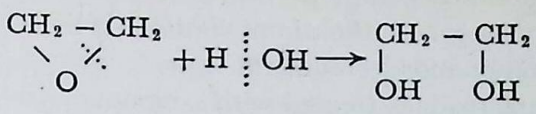
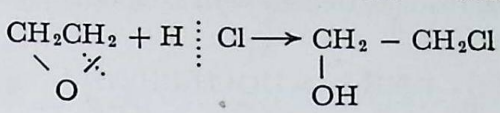
Thus the reactions with water, mentioned on p. 199, and with hydrochloric acid are

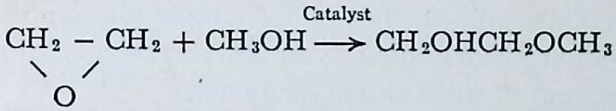




The reaction between ethylene oxide and Grignard reagents has already been considered (p. 161).

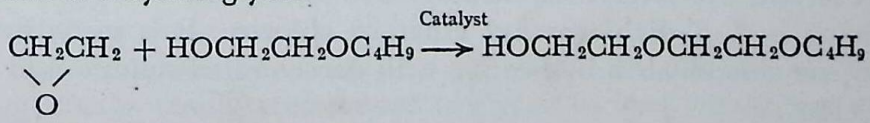
Commercial Products from Ethylene. We have pointed out previously that ethylene is the starting material for the synthesis of a large number of chemicals of industrial importance. At this time we shall consider a few of those products which are closely related to ethylene glycol. These compounds are generally made from ethylene oxide, which, as we have seen, is obtained from ethylene.

If ethylene oxide is treated with an alcohol in the presence of a small amount of a catalyst the two combine and a compound which is both an ether and an alcohol results.



The **monomethyl ether of ethylene glycol,** $CH_2OHCH_2OCH_3$, the monobutyl ether, $CH_2OHCH_2OC_4H_9$, and similar compounds are readily prepared in this way. They are marketed under the name of *Cellosolve*. Thus the monomethyl ether is called **Methyl cellosolve,** and the monobutyl ether is called **Butyl cellosolve.** The former boils at 124°, the latter at 170.6°. These substances are useful solvents because they are at one and the same time both alcohols and ethers, and for this reason readily dissolve a great variety of organic compounds. They are also miscible with water up to and including Butyl cellosolve.

Closely related compounds are the ethers of diethylene glycol, $CH_2OHCH_2OCH_2CH_2OH$; they are known as the *carbitols*. The carbitols are prepared by the action of ethylene oxide on the monoethers of ethylene glycol.



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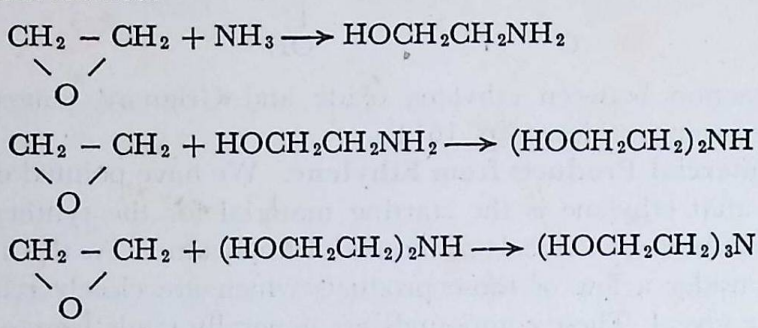
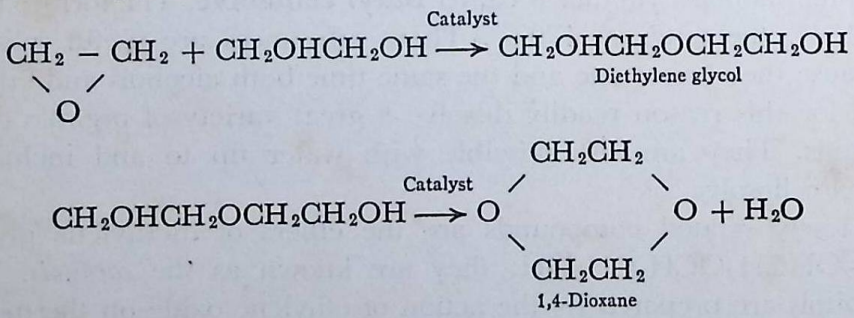
Butyl carbitol, boiling at 222°, is particularly interesting as it is an excellent solvent and is completely miscible with water. It can be used for preparing homogeneous solutions containing both water and complex organic compounds insoluble in water.

When ethylene oxide is treated with ammonia, a mixture of amino alcohols is formed.



These compounds are marketed under the names of the *ethanolamines*. The final product of the reaction is known as *triethanolamine*. They are high-boiling, colorless, viscous liquids, alkaline in reaction, hygroscopic and miscible with water in all proportions. Their base strength is comparable to that of the simple aliphatic amines. The ethanolamines are widely used as emulsifying agents, in the preparation of soaps, and to some extent as solvents.

Still another solvent which may be prepared from ethylene and which is related to ethylene glycol is a compound known as 1,4-*dioxane*. It is a liquid boiling at 102° and is miscible with water. It can be prepared by the dehydration of diethylene glycol, which in turn is prepared from glycol and ethylene oxide.



A solvent which has been mentioned in connection with petroleum refining is β, β'-**dichloroethyl ether** or **chlorex.** It is made from ethylene chlorohydrin by heating with concentrated sulfuric acid at 90°–100°.

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$$CH_2ClCH_2O \boxed{H + HO} CH_2CH_2Cl \longrightarrow \underset{\beta,\beta'\text{-Dichloroethyl ether}}{CH_2ClCH_2OCH_2CH_2Cl} + H_2O$$

Divinyl ether, $CH_2 = CH - O - CH = CH_2$ (bp 28.3°), may be prepared from β,β'-dichloroethyl ether by heating it with solid potassium hydroxide.

$$CH_2ClCH_2OCH_2CH_2Cl + 2KOH \longrightarrow (CH_2 = CH)_2O + 2KCl + 2H_2O$$

Divinyl ether is used as a general anesthetic, and in some respects it is claimed to be better than ether. This compound is related both to ethylene and diethyl ether, two substances which are widely used in anesthesia.

Other Glycols. Two other glycols are worthy of mention. **Propylene glycol,** $CH_3CHOHCH_2OH$, can be prepared from propylene by exactly the same reactions as are used in the preparation of ethylene glycol from ethylene. It resembles ethylene glycol in its physical properties but differs from it chemically in that it is a *secondary* as well as a primary alcohol. **Trimethylene glycol,** $CH_2OHCH_2CH_2OH$, is a byproduct of the preparation of glycerol from fats. It is a viscous liquid boiling at 214° and miscible with water in all proportions. The corresponding dibromide may be prepared from it by the action of hydrobromic acid. This dibromide is known as *trimethylene dibromide*, $CH_2BrCH_2CH_2Br$; we shall have occasion to refer to it again in connection with the synthesis of certain compounds.

General Methods of Preparing Glycols. The general methods of preparing glycols depend on the relative position of the hydroxyl groups. When the two groups are on adjacent carbon atoms, there are other methods which can be employed besides the ones outlined above. In general, the corresponding olefin is the starting material. For example, hydrogen peroxide and a catalyst, such as osmium tetroxide, will oxidize ethylene and its derivatives to 1,2-glycols.

$$CH_2 = CH_2 + H_2O_2 \xrightarrow{\text{Catalyst}} CH_2OHCH_2OH$$

This reaction is carried out best in tertiary butyl alcohol as the solvent. It is somewhat analogous to the oxidation of olefins to glycols by potassium permanganate (p. 60).

A number of relatively complex compounds containing an ethylenic linkage can be readily transformed to glycols by lead tetracetate.

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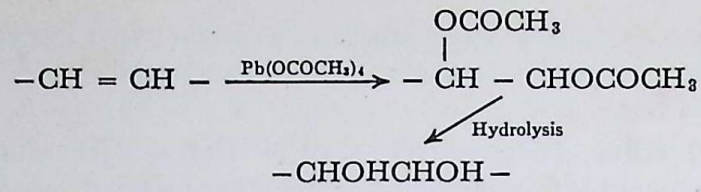

When the two hydroxyl groups are on the extreme ends of the carbon chain the glycol can be prepared from the ethyl ester of the corresponding dibasic acid by reduction with sodium and alcohol or by catalytic hydrogenation. This is merely an application of a general method of preparing primary alcohols from esters (p. 98); it is illustrated below in the preparation of tetramethylene glycol.

Since acids of the general formula $(CH_2)_n(COOH)_2$ are readily available (Chap. 11), the corresponding glycols, $CH_2OH(CH_2)_nCH_2OH$, can be easily prepared. The physical properties of some of the members of such a series of glycols are given in the table which follows.

PHYSICAL PROPERTIES OF GLYCOLS, $CH_2OH(CH_2)_nCH_2OH$

Name	*Formula*	*Boiling Point*	*Melting Point*	*Density*
Ethylene glycol	CH_2OHCH_2OH	197.4°	−16°	1.1097(25°)
Trimethylene glycol	$CH_2OHCH_2CH_2OH$	214°	—	1.0526(18°)
Tetramethylene glycol	$CH_2OH(CH_2)_2CH_2OH$	230°	16°	1.020(20°)
Pentamethylene glycol	$CH_2OH(CH_2)_3CH_2OH$	239°	—	0.994(18°)
Hexamethylene glycol	$CH_2OH(CH_2)_4CH_2OH$	250°	42°	
Heptamethylene glycol	$CH_2OH(CH_2)_5CH_2OH$	262°	22.5°	

The first four members are all miscible with water and alcohol. The solubility in water decreases as the molecular weight increases.

Nomenclature. The names which are commonly assigned to the compounds we have been discussing are either trivial names which originated from the method of preparation, or trade names which have been recently established. Glycols which belong to the series given in the table are named as indicated, but this method applies only to this special group of glycols. By the Geneva system the glycols are named from the corresponding saturated hydrocarbons, adding the suffix *diol* and indicating by numbers the position of the groups. Thus

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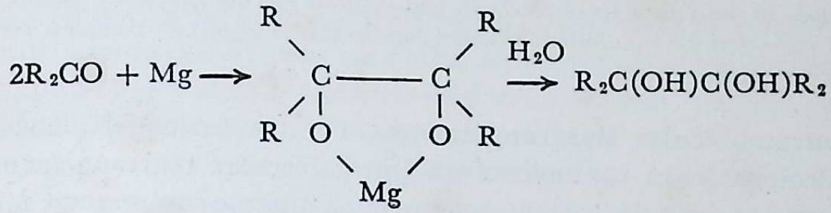
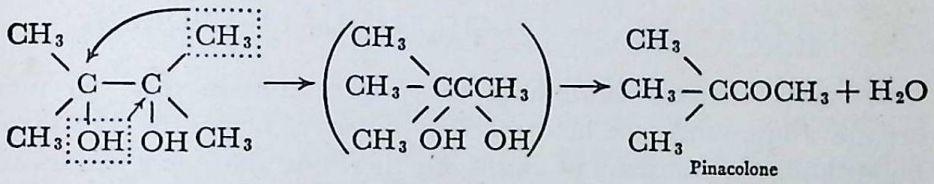
propylene glycol is propanediol-1,2; trimethylene glycol is propanediol-1,3. The nomenclature of the corresponding halogen compounds has already been considered (p. 156).

Pinacols. The glycols which have two adjacent hydroxyl groups and four alkyl groups symmetrically arranged can be prepared by the reduction of ketones in alkaline medium (p. 135). The simplest of these is **pinacol,** $(CH_3)_2COHCOH(CH_3)_2$, which is prepared from acetone. It is a liquid boiling at 172°; it forms a white, crystalline hydrate when treated with water. Similar compounds can be prepared by the reduction of other ketones with metallic magnesium.



Pinacol Rearrangement. The pinacols are of interest because of a remarkable reaction which takes place when they are heated with acids. A molecule of water is eliminated, a **rearrangement of the alkyl groups** takes place, and a ketone is formed.



We do not know the mechanism of the process by which pinacol is transformed to pinacolone; the parenthesized intermediate is hypothetical and has never been isolated.

The structure of the rearrangement product, pinacolone, is known. On treatment with sodium hypobromite, pinacolone furnishes bromoform and trimethylacetic acid.

$$(CH_3)_3CCOCH_3 + 3NaOBr \longrightarrow (CH_3)_3CCOONa + CHBr_3 + 2NaOH$$

The structure of trimethylacetic acid has been established in a number of ways. One of these, the reaction between carbon dioxide and the Grignard reagent from *t*-butyl chloride, is shown.

$$(CH_3)_3CCl \xrightarrow[\text{Ether}]{Mg} (CH_3)_3CMgCl \xrightarrow{CO_2} (CH_3)_3CCOOMgCl \xrightarrow{HCl} (CH_3)_3CCOOH$$

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Unlike the rearrangement of *n*-butane to isobutane which occurs only at high temperatures and in the presence of special catalysts, the pinacol rearrangement occurs at 25° in the presence of any one of a variety of catalysts. Furthermore, unlike the hydrocarbon rearrangement, the pinacol rearrangement runs to completion. The high rate of this reaction at room temperature with a variety of catalysts is closely related to the specific structure involved. The question of rate must not be confused with the fact that the reaction goes to completion. We only rarely encounter rearrangements which take place at 25° and which are balanced equilibria. This is indeed fortunate for, if rearrangements under these conditions were the rule rather than the exception, the elucidation of structure would be an almost hopeless job.

The heat evolved in the pinacol rearrangement, like that in the interconversion of the butanes, is small. The process involves the transformation of one molecule of reactant to two molecules of products, and accurate calculations using specific heat data show that the equilibrium constant corresponds to essentially complete conversion.

Intramolecular Rearrangements. The conversion of pinacol to pinacolone is an example of an intramolecular rearrangement, a process in which the carbon skeleton of an organic compound changes or a substituent changes its position. Two rearrangements have already been encountered. They are

(1) $CH_3CH_2CH_2CH_3 \rightleftharpoons CH_3CH(CH_3)_2$, and

(2) $CH_3CH_2CH_2NH_2 \xrightarrow{HNO_2} CH_3CH_2CH_2OH + CH_3CHOHCH_3$

We have stressed throughout the presentation in this text that organic compounds are held together by covalent bonds, that these bonds hold specific pairs of atoms together, and that, as a result, we have structure and isomerism in organic compounds. The occurrence of intramolecular rearrangements does not invalidate these concepts and conclusions. It does mean that **certain organic structures are unstable under certain experimental conditions.** This instability is relieved in perfectly definite, not random, ways; the course of intramolecular rearrangements is just as definite and regular as those of the more conventional reactions. Pinacol always rearranges to pinacolone; it does not furnish pinacolone on one occasion and some other product on another.

We shall see that rearrangements are extremely useful in much organic synthetic work; and, odd though it may seem at this time, they are most useful in determining structure. (Compare the discussion on p. 495.) We shall encounter many more examples of intramolecular rearrangements later. Here it is essential only to empha-

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size that rearrangements are not strange and abnormal phenomena; they are just as normal processes for certain structures as are the conventional reactions of organic chemistry for other structures.

GLYCEROL

Glycerol or, as it is often called, *glycerine*, is a trihydroxy derivative of propane having the formula $CH_2OHCHOHCH_2OH$. It is formed whenever an animal fat or a vegetable oil is boiled with sodium hydroxide. If we take a typical animal fat, such as tallow from the beef animal, and boil it with sodium hydroxide, it changes into a thick mass which with sufficient water will form a clear solution. On adding sulfuric acid to this solution we obtain a precipitate which consists of a mixture of two acids of the fatty acid series, namely, palmitic acid, $C_{15}H_{31}COOH$, and stearic acid, $C_{17}H_{35}COOH$. Since these acids are insoluble in water, they separate when the solution of their sodium salts is made acid. If we evaporate the water solution, we find that after distilling all the water a viscous high-boiling liquid remains together with sodium sulfate. This liquid is **glycerol.** It can be purified by distillation under diminished pressure.

The industrial preparation of glycerol is essentially that just outlined. It is thus a byproduct of the manufacture of the fatty acids or their salts—the soaps. It has also been manufactured by the fermentation of sugar by yeast under special conditions. The mixture is kept somewhat alkaline and sodium bisulfite is added during the fermentation. During World War I very large quantities of glycerol were prepared in this way in Germany. It has been sold as an antifreeze for automobile radiators. It is used in the manufacture of cosmetics, dentifrices, and in the preparation of inks and mucilages.

Physical and Chemical Properties. Glycerol is a viscous, nontoxic, colorless liquid with a sweetish taste. It is miscible in all proportions with water. When pure it can be made to solidify by cooling; the crystals melt at 17°. The liquid is prone to supercool and it is often extremely difficult to start crystallization. The usual samples of glycerol contain varying proportions of water since glycerol is hygroscopic. It boils at 290°. If kept long at its boiling point, it undergoes partial decomposition, and is therefore best purified by distillation under diminished pressure.

Glycerol contains two primary and one secondary hydroxyl group. The presence of three hydroxyl groups in the molecule is established by the fact that, when acylated, three acyl groups are introduced. As

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an example of this the preparation of the triacetate may be given.

$$\begin{array}{l} CH_2OH \\ | \\ CHOH \\ | \\ CH_2OH \end{array} + 3(CH_3CO)_2O \longrightarrow \begin{array}{l} CH_2OCOCH_3 \\ | \\ CHOCOCH_3 \\ | \\ CH_2OCOCH_3 \end{array} + 3CH_3COOH$$

Glycerol triacetate (triacetin)

When treated with gaseous hydrochloric acid one or both of the primary hydroxyl groups are replaced by chlorine. The products are called glycerol chlorohydrins.

$$CH_2OHCHOHCH_2OH \xrightarrow{HCl} CH_2ClCHOHCH_2OH \xrightarrow{HCl} CH_2ClCHOHCH_2Cl$$

Glycerol monochlorohydrin

α,γ-Glycerol dichlorohydrin

The structure of the final product is established by the fact that on oxidation it yields a *ketone*, dichloroacetone, $CH_2ClCOCH_2Cl$.

Nitroglycerine and Dynamite. The trinitrate of glycerol is called *nitroglycerine*. It has the formula $CH_2(ONO_2)CH(ONO_2)CH_2(ONO_2)$. This ester is an oily liquid which solidifies at 12°. It is a powerful explosive which is very sensitive to shock and dangerous to transport. Nobel[1] discovered in 1867 that if nitroglycerine was absorbed by some inert porous material such as kieselguhr (silica), a powerful but relatively safe explosive was formed. This was *dynamite*. Dynamite today is commonly manufactured by using wood pulp or sawdust as the solid absorbent materials and adding ammonium nitrate.

Nitroglycerine is prepared by the action of concentrated nitric and sulfuric acids on glycerol. The temperature must be carefully controlled.

$$C_3H_5(OH)_3 + 3HNO_3 \overset{H_2SO_4}{\rightleftharpoons} C_3H_5(ONO_2)_3 + 3H_2O$$

FATS AND OILS

Having now considered the chemistry of glycerol, we are in a position to attack the complicated subject of the fats and oils. First of all, a word of warning is necessary about the use of the term *oil*. It is a much abused expression and originally probably connoted merely a somewhat viscous liquid; for example, sulfuric acid was called *oil of*

[1] A. B. Nobel (1833–1896). A Swedish chemist and pioneer in the field of explosives. He dedicated his fortune to the establishment of the Nobel prizes.

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vitriol. The organic substances which are commonly called *oils* can be divided into three classes: (1) **mineral oils,** which are petroleum products; (2) **essential oils,** which are fragrant, volatile constituents of plants and plant products (e.g., oil of wintergreen, oil of cinnamon, oil of cloves); (3) **vegetable oils,** which are esters of glycerol. The vegetable oils together with the animal fats form a distinct class which we are now to consider. Generally speaking, if a member of this class is liquid at room temperature, it is called an *oil* and if solid, a *fat*. Cocoanut oil and palm oil are liquids at temperatures which prevail in the tropics where they are obtained but they are solids at usual room temperature in the temperate zone.

The Acids Obtained from Fats and Oils. When tallow is hydrolyzed by the action of sodium hydroxide, a mixture of acids which consists predominantly of stearic and palmitic acids is obtained. If we examine in a similar way other animal fats and oils, we always find glycerol and a mixture of acids as the products of saponification. The more important of these acids are listed below in the table, together with their physical properties.

THE ACIDS WHICH OCCUR COMMONLY IN FATS AND OILS

Name	*Formula*	*Structure*	*Melting Point*
Palmitic acid	$C_{15}H_{31}COOH$	$CH_3(CH_2)_{14}COOH$	63°
Stearic acid	$C_{17}H_{35}COOH$	$CH_3(CH_2)_{16}COOH$	69°
Oleic acid	$C_{17}H_{33}COOH$	$CH_3(CH_2)_7CH{=}CH(CH_2)_7COOH$	14°
Linoleic acid	$C_{17}H_{31}COOH$	$CH_3(CH_2)_4CH{=}CHCH_2CH{=}CH(CH_2)_7COOH$	$<0°$
Linolenic acid	$C_{17}H_{29}COOH$	$CH_3CH_2CH{=}CHCH_2CH{=}CHCH_2CH{=}CH(CH_2)_7COOH$	$<0°$

The last three acids are unsaturated acids which contain the same carbon skeleton (seventeen carbon atoms and a carboxyl group) as stearic acid. Four separate homologous series of acids with different general formulas are represented. Palmitic and stearic acids, which belong to the fatty acid series, have the general formula $C_nH_{2n+1}COOH$; oleic acid has the formula $C_nH_{2n-1}COOH$, linoleic $C_nH_{2n-3}COOH$, and linolenic $C_nH_{2n-5}COOH$.

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Glycerides. The esters of an acid with glycerol are called *glycerides*. They may be simple glycerides, that is, glycerol esterified with three molecules of the same acid; or they may be mixed glycerides in which one molecule of glycerol has been esterified with two, or even three, different acids. The fats and oils are almost always composed of mixed glycerides.

The simple glycerides are named as follows: **triacetin** is the tri-acetic ester of glycerol; **tripalmitin** is the tri-palmitic ester of glycerol; **triolein** is the tri-oleic ester of glycerol. The general formula is

$$\begin{array}{c} RCOOCH_2 \\ | \\ RCOOCH \\ | \\ RCOOCH_2 \end{array}$$

The melting points of some common glycerides are given below:

	Melting Point
Tripalmitin	60°
Tristearin	71°
Triolein	17°
Trilinolein	Oil below 0°

The glycerides of the saturated acids, like the free acids themselves, melt at a much higher temperature than the glycerides of the unsaturated acids. Thus, the relatively low melting point of a vegetable oil, in comparison to that of an animal fat, is due to the fact that the former contains unsaturated glycerides. The essential difference between tallow and cottonseed oil is the absence of a few hydrogen atoms in the latter.

Hydrogenation of Vegetable Oils. A large industry exists which transforms vegetable oils into solid fats. The chemistry of this process is extremely simple. It is based on the reaction known as *catalytic hydrogenation* which we have already considered (p. 56). The following reaction illustrates the transformation of triolein to tristearin.

$$\begin{array}{l} CH_3(CH_2)_7CH = CH(CH_2)_7COOCH_2 \\ \qquad\qquad\qquad\qquad\qquad\qquad\qquad\quad | \\ CH_3(CH_2)_7CH = CH(CH_2)_7COOCH \\ \qquad\qquad\qquad\qquad\qquad\qquad\qquad\quad | \\ CH_3(CH_2)_7CH = CH(CH_2)_7COOCH_2 \end{array} \xrightarrow[\text{Ni at } 200^\circ]{+3H^2} \begin{array}{l} CH_3(CH_2)_{16}COOCH_2 \\ \qquad\qquad\qquad\qquad\qquad\qquad\qquad\quad | \\ CH_3(CH_2)_{16}COOCH \\ \qquad\qquad\qquad\qquad\qquad\qquad\qquad\quad | \\ CH_3(CH_2)_{16}COOCH_2 \end{array}$$

The hydrogenation of vegetable oils is controlled in order to yield the type of product desired. Thus, if a synthetic lard is wanted for cooking purposes, the reduction is stopped when partially complete;

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APPROXIMATE COMPOSITION OF SOME FATS AND OILS

Name	*Tristearin and Tripalmitin*	*Triolein*	*Trilinolein*	*Other Glycerides*
	Per cent	Per cent	Per cent	Per cent
Tallow	75	25	0	0
Butter fat (There is some tributyrin in this fat.)	53	39	0	8
Olive oil	25	70	5	0
Cottonseed oil	25	25	47	3
Linseed oil*	8	18	30	44
Soybean oil	7	33	52	8
Tung oil**	5	13		82

* Contains about 30 per cent of the glycerides of linolenic acid.

** Contains about 73 per cent of eleostearic acid, $C_{17}H_{29}COOH$, which is isomeric with linolenic acid.

otherwise a material comparable to tallow is obtained. The term *hardening* is sometimes given to this process of hydrogenating a vegetable oil.

If the reduction is carried past the formation of saturated glycerides, these glycerides, since they are esters, undergo reduction to alcohols (see pp. 98–204). This reduction furnishes glycerol and the long-chain alcohols corresponding to the acids present in the glycerides. It is an important source of the C_{12}, C_{16}, and C_{18} alcohols.

$$\begin{array}{l} CH_3(CH_2)_{16}COOCH_2 \\ \quad\quad\quad\quad\quad\quad | \\ CH_3(CH_2)_{16}COOCH \\ \quad\quad\quad\quad\quad\quad | \\ CH_3(CH_2)_{16}COOCH_2 \end{array} + 6H_2 \xrightarrow{\text{Catalyst}} 3CH_3(CH_2)_{16}CH_2OH + \begin{array}{l} CH_2OH \\ | \\ CHOH \\ | \\ CH_2OH \end{array}$$

If a suitable catalyst is used, glycerides of the unsaturated acids can be reduced to glycerol and long-chain unsaturated alcohols.

Butter. Butter differs from most other fats in that it contains the glycerides of a large number of different acids. Among these acids is butyric acid. When butter has stood for some time it slowly becomes rancid because of the liberation of free butyric acid by the hydrolysis of the glyceride. Although only a very small per cent of the glyceride may be decomposed, the butter is quite unfit for use because of the disagreeable smell of butyric acid. The butyric acid may be removed by washing the butter with an aqueous solution of sodium bicarbonate, or by blowing steam through the molten butter which volatilizes the butyric acid. Butter thus freed from butyric acid is called *renovated butter*. In order to restore to it some of the characteristic flavor and consistency of natural butter, it is usually churned with skim milk under such

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conditions that it separates in more or less of a conglomerate containing considerable amounts of water.

Oleomargarine and various vegetable butters and other butter substitutes are mixtures of vegetable oil and animal fats or partially hydrogenated vegetable oils of such consistency as to resemble butter. To simulate the mechanical structure of butter and its characteristic flavor such substances are often agitated with milk before being put on the market. They must be artificially colored. In many states, to prevent fraud, there are special laws covering the sale of oleomargarine and other special butters.

Candle Stock. A mixture of palmitic and stearic acids is prepared industrially and sold under the name of *stearin.* It is a waxlike solid, used for the manufacture of candles and sometimes called *candle stock.* For the preparation of this substance animal fats or hydrogenated oil must obviously be used, since only the high-melting acids obtained from saturated glycerides yield a solid material suitable for candles.

Hydrolysis of Fats. The hydrolysis of fats to produce the free acids is brought about by heating with a catalyst and water. The catalyst used is usually either a small amount of lime or a complex organic acid known as *Twitchell's reagent.* The reaction goes to completion, probably because the acids are insoluble and separate from the mixture and because a large excess of water is used. The solution from which the insoluble acids have been separated is distilled and glycerol is obtained.

$$\begin{array}{l} RCOOCH_2 \\ | \\ RCOOCH \\ | \\ RCOOCH_2 \end{array} + 3H_2O \xrightarrow[\text{100°}]{\text{Catalyst}} 3RCOOH + \begin{array}{l} CH_2OH \\ | \\ CHOH \\ | \\ CH_2OH \end{array}$$

Manufacture of Soap. Soap is prepared by heating animal fats and vegetable oils with sodium hydroxide. When the reaction is complete, salt is added which causes the complete separation of the sodium salts of the fatty acids: these are lighter than water, float on the surface, and are removed. The glycerol in the residual brine may be obtained by distillation.

$$\begin{array}{l} RCOOCH_2 \\ | \\ RCOOCH \\ | \\ RCOOCH_2 \end{array} + 3NaOH \longrightarrow \underset{\substack{\text{Soap} \\ \text{"salted out"} \\ \text{with brine}}}{3RCOONa} + \begin{array}{l} CH_2OH \\ | \\ CHOH \\ | \\ CH_2OH \end{array}$$

The soaps which come on the market are the sodium salts of the fatty acids mixed with a number of other materials which give them odor, color, and cleansing properties. The hydrogenated vegetable oils are

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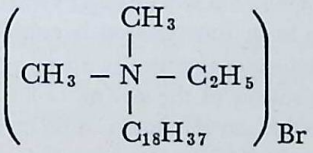
much used in soap manufacture. A satisfactory soap cannot be made from an oil like cottonseed oil itself, but after hydrogenation the oil is the equivalent of tallow.

Rosin is also used in the manufacture of soaps. It is the amorphous yellow residue left after the distillation of *spirits of turpentine* from the sap of coniferous trees. It is an organic acid (or acid anhydride) of high molecular weight (p. 596) and, therefore, reacts with bases to form salts. Solutions of sodium "rosinate" have cleansing power and produce lather like soap solutions. Many cheap laundry soaps contain much rosin. Shaving soap usually contains some rosin to produce good lather; it also contains glycerol and gum to prevent too rapid drying.

Detergents and Their Mode of Action. In recent years many other materials have become available which have the cleansing action of the ordinary soaps but which are quite different in structure. The alkali salts of the alkylsulfuric acids having ten or more carbon atoms in the molecule are detergents. Sodium laurylsulfate, $CH_3(CH_2)_{10}CH_2OSO_3Na$, is representative. The alcohols used are obtained by the hydrogenation of the fats and oils (p. 211). The sodium alkylsulfates may be used in slightly acid solutions (which would precipitate the fatty acids from ordinary soaps), and in salt water and hard water since the calcium and magnesium alkylsulfates are soluble.

Another group of detergents consists of the invert soaps or cation active soaps. These are quaternary ammonium salts containing at least one large alkyl group. Dimethyl-ethyl-octadecyl-ammonium bromide is representative.



The name follows from the fact that the active portion of the molecule is the cation, just the reverse of the other classes of detergents. Certain invert soaps possess remarkable bactericidal effectiveness.

A third group of detergents is obtained from polyhydroxy compounds by partial esterification with a fatty acid of large molecular weight. Esterification of one hydroxyl group, for example, in pentaerythritol with stearic acid furnishes a typical member of the group, $(HOCH_2)_3CCH_2OCOC_{17}H_{35}$.

These three classes of detergents by no means exhaust the field (compare p. 425); they do furnish sufficient background for an ele-

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mentary discussion of the way in which detergents work. Detergents lower the surface tension of water. Their water solutions, therefore, will more readily than pure water wet the particles of dirt which are to be removed. The detergents all contain one group which confers water solubility, a hydrophilic group, and one which has just the opposite effect, a hydrophobic group. In the ordinary soaps the hydrophilic group is carboxyl, while the hydrophobic group is the long alkyl group; in the sodium alkylsulfates the hydrophilic group is sulfate, while the hydrophobic group is again the long-chain alkyl. In water the detergents emulsify oil, grease, and dirt, presumably by surrounding these individual foreign particles in such a way that the hydrophobic end of the detergent is near the emulsified particle and the hydrophilic end of the detergent is in the water.

DRYING OILS

Drying of Oil Paints Is Oxidation. Linseed oil and certain other vegetable oils, such as tung and soybean oil, slowly absorb oxygen from the air and change to hard transparent solids. This property is particularly manifested if a thin layer of the oil is spread on some surface such as wood which is exposed to the air. This oxidation of linseed oil is commonly and quite erroneously called *drying*. It is the basic chemical reaction in the so-called drying of oil paints.

The linseed oil as it comes from the flax seed (called *raw linseed oil*) absorbs oxygen very slowly; paint made from it would be too slow drying for most purposes. If linseed oil is heated to 200° in the presence of certain heavy metal salts it undergoes a chemical change as a result of which it will absorb oxygen much more rapidly at room temperature. Oil which has been thus treated is called *boiled linseed oil* and is the material used in the manufacture of practically all oil paints.

Our knowledge of the chemistry of the drying of linseed oil is very meager. The ability of an oil to combine with oxygen seems to be connected with the presence of glycerides of highly unsaturated acids such as linolenic acid. We always find a high percentage of such glycerides in oils which have drying properties. It is probable that the oxygen of the air combines with the unsaturated linkages and that a polymerization somewhat analogous to the polymerization of isoprene then takes place. If this is true, dried paint is a polymerized, oxidized glyceride of linolenic acid.

Oil Paints. Oil paints are suspensions of very finely divided pigments in linseed oil. The pigments are for the most part inorganic compounds such as basic lead carbonate (white lead), lead oxide (red lead), etc. When an especially quick-drying oil paint is desired the oil is sometimes diluted with spirits of turpentine which really dries in the sense that it evaporates and leaves a thin coating of the

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material behind; this then "dries" by absorbing oxygen in the usual manner. Certain substances called *driers* are sometimes added to the paint. They act catalytically to accelerate the oxidation process.

Oilcloth is made by covering cloth with boiled linseed oil and letting it dry. Linoleum is a "dried" mixture of linseed oil and cork which have been pressed together. Tung oil is also used for the same purpose.

There is a great distinction between oil paints, which we have just been discussing, and various other forms of paint or paintlike substances, such as shellac, varnishes, and lacquers. These latter substances are solutions of organic materials in volatile solvents, and their drying is due to the evaporation of the solvent, the organic material being left behind as a thin coating. For many purposes lacquers of various sorts are now replacing oil paints. Automobiles, for example, and many other metal surfaces are painted with a lacquer prepared from cellulose.

Analysis of Fats and Oils. Certain convenient methods of analysis are frequently employed in studying fats and oils. By saponifying a weighed sample of the material with potassium hydroxide, the **saponification number** may be obtained. It is defined as the number of milligrams of potassium hydroxide required to saponify 1 g of fat. The saponification number reflects the average molecular weight of the glycerides present in the sample. A large saponification number indicates the presence of glycerides of the lower fatty acids.

The degree of unsaturation of a fat or oil can be determined by allowing a known weight of the material to react with iodine in a solution of mercuric chloride in alcohol. The amount of halogen which combines with the double linkages of the various unsaturated glycerides can be readily determined. It should be noted carefully, however, that the direct combination of iodine with double linkages is very slow; addition proceeds in this instance at a convenient rate because of the special reagent employed. The results are expressed as the **iodine number,** *which is the number of grams of iodine combining with* 100 *g of fat.* This number is obviously greater the more unsaturated glycerides are present. Typical iodine numbers are given in the tables below.

IODINE NUMBER OF FATTY ACIDS AND THEIR GLYCERIDES

	Free Acid	*Glyceride*
Oleic	90.0	86.2
Linoleic	181.4	173.5
Linolenic	274.1	262.1

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IODINE NUMBER OF CERTAIN FATS AND OILS

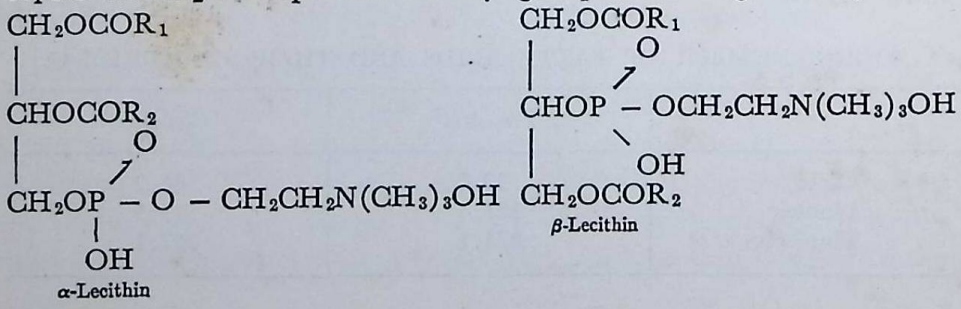
Tallow	35–40	Cottonseed oil	104–116
Lard	48–64	Soybean oil	135–150
Olive oil	77–91	Tung oil	150–170
		Linseed oil	175–201

Reichert-Meissl Number. Butter contains a relatively large amount of the glycerides of the lower fatty acids; artificial butters and renovated butters contain much less. It is, therefore, important to have a method of determining the percentage of the glycerides of the lower fatty acids in a sample of butter or other fat. This is done by saponifying 5.5 g of the fat, acidifying with sulfuric acid, and distilling the aqueous solution until a definite volume of distillate is collected. The lower fatty acids are volatile with steam and are largely in the distillate. The number of cubic centimeters of 0.1 *N* potassium hydroxide required to neutralize this distillate is the Reichert-Meissl number of the fat.

In addition to the tests we have described, the analyst makes use of a variety of specific tests, such as color reactions, given by individual fats and oils. A pure fat or oil, it must be realized, is not a pure compound, but a complex mixture of glycerides. Different pure samples of the same fat or oil will not give identical numerical values in the tests, but the values for a given fat or oil will fall in a definite range. Consequently the analyst's task is an art.

Phosphatides. A group of glycerides closely rated to the fats and oils is known as the *phosphatides*. They occur widely distributed in animal and plant cells but usually in small amounts. They may be regarded as fats in which one acyl group has been replaced by a complex phosphoric acid. Like the fats, they usually are present in nature as a mixture of several compounds containing different closely related acyl groups (e.g., stearyl and palmityl). For this reason probably no representative of the phosphatides has been obtained in a pure state.

The **lecithins** (α and β) are the commonest phosphatides. Their structures are usually represented by the following formulas. where R_1CO and R_2CO represent the acyl groups of the higher fatty acids.



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On hydrolysis the lecithins yield glycerol, a mixture of fatty acids, phosphoric acid, and the quaternary base, choline, $CH_2OHCH_2(CH_3)_3NOH$ (p. 196). Large amounts of the lecithins are found in egg yolk, liver, and brain. Like the fats they are soluble in ether and many other organic solvents, but insoluble in water.

Waxes. A group of plant and animal products having somewhat the same physical properties and solubilities as the fats are the **waxes.** They are entirely different, however, in their chemical composition and reactions. Waxes are usually mixtures of higher alcohols of the methyl alcohol series ($C_nH_{2n+1}OH$) with esters of these same alcohols and the fatty acids; in some waxes, higher paraffin hydrocarbons are also present. Waxes may be distinguished from the fats by the fact that when boiled with sodium hydroxide they are not transformed into water-soluble products. (The higher alcohols are, of course, insoluble in water and aqueous sodium hydroxide.) Together with sterols (Chap. 30) they are the "unsaponifiable portion" left when a chloroform or ether extract of plant or animal tissue is hydrolyzed with alkali. (The esters of the higher alcohols present in the waxes are converted to the higher alcohols themselves by this treatment, of course.)

The alcohols, $C_{30}H_{61}OH$, **myricyl alcohol,** and $C_{26}H_{53}OH$, **ceryl alcohol,** are frequently found in waxes. **Beeswax** is largely myricyl palmitate, $C_{15}H_{31}COOC_{30}H_{61}$. It is widely used in the manufacture of polishes and in pharmaceutical preparations. **Chinese insect wax** is obtained from a deposit made by a parasitical insect on certain trees in Asia. It is largely ceryl cerotate, $C_{25}H_{51}COOC_{26}H_{53}$. (Cerotic acid is $C_{25}H_{51}COOH$.) **Carnauba wax** has an exceptionally high melting point (83° to 86°). It is extracted from the leaves of a Brazilian palm. It is largely $C_{26}H_{51}COOC_{30}H_{61}$.

Higher Polyhydric Alcohols. Alcohols having four, five, and six hydroxyl groups are known. Many of these are found in nature. **Erythritol,** $CH_2OH(CHOH)_2CH_2OH$, occurs, usually as an ester, in many lichens and fungi. The tetranitrate of erythritol is used in medicine for certain cardiac disturbances. **Arabitol, xylitol,** and **adonitol** are pentahydric alcohols. They all may be represented by the formula $CH_2OH(CHOH)_3CH_2OH$. The hexahydric alcohols, **mannitol, dulcitol,** and **sorbitol,** $CH_2OH(CHOH)_4CH_2OH$, also occur in nature.

In general the higher polyhydric alcohols are sweet, crystalline compounds, readily soluble in water. Their reactions are those which would be predicted from a knowledge of the simpler polyhydric alcohols. Thus on acylation with acetic anhydride, the pentahydric

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alcohols form pentaacetates, the hexahydric alcohols, hexaacetates. The close relationship of these higher polyhydric alcohols to the sugars will be evident later (Chap. 15).

QUESTIONS AND PROBLEMS

1. A sample of an organic compound is known to be either 1,2-dihydroxypentane, 2,4-dihydroxypentane, or 1,5-dihydroxypentane. What chemical tests would you use to establish the identity of the material?

2. Compare the structural formulas and the chemical and physical properties of the following five naturally occurring materials: tristearin, carnauba wax, arabitol, triolein, lecithin.

3. Write structural formulas for tetramethylene glycol, pinacol, glycerol α-monochlorohdrin, erythritol, and triacetin.

4. Indicate the steps in the synthesis of $CH_3CH_2OCH_2COOH$ from CH_3CH_2OH.

5. Can you offer an explanation for the fact that the cellosolves and carbitols are soluble both in water and in organic solvents?

6. How are 1,4-dioxane and β,β'-dichloroethyl ether prepared?

7. Write balanced equations for the conversion of triolein to tristearin indicating the experimental conditions to be used.

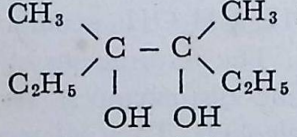
8. What experiments would you use to distinguish (*a*) cottonseed oil from a mixture of tallow and linseed oil, (*b*) butter from a mixture of cottonseed oil and lard, and (*c*) cottonseed oil from a sample of a mineral oil?

9. Upon what chemical reaction does the "drying" of such oils as linseed depend?

10. Define and illustrate the terms (*a*) *polyfunctional compound*, (*b*) *detergent*, (*c*) *intramolecular rearrangement*, (*d*) *dynamite*, (*e*) *rosin*.

11. Describe briefly the manufacture of soap. Compare the structure of soap with those of some other detergents.

12. Write equations for (*a*) the rearrangement of pinacol to pinacolone, (*b*) the preparation of



from ethyl alcohol, (*c*) three industrially important reactions of ethylene oxide.

13. Show the reactions for the conversions: (*a*) acetone to trimethylacetic acid, (*b*) oleic acid to ethyl stearate, (*c*) acetylene to glyoxal, (*d*) lecithin to glycerol, (*e*) glycerol to symmetrical dichloroacetone.

14. Write balanced equations for the transformation of (*a*) $\underset{\diagdown\ \diagup}{\underset{O}{CH_2CH_2}}$ to $(CH_3)_2NOCH_2CH_2OH$, (*b*) $(CH_3)_2COHCHOHCH_3$ to acetone and acetal-

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dehyde, (*c*) $(CH_3)_2CHCH_2CHO$ to $(CH_3)_2CHCOCHO$, (*d*) $CH_3COCOOH$ to CH_3COOH, (*e*) CHOCHO to $CH_2OHCOOH$.

15. A chloroform extract of a certain natural product was known to contain free fatty acids, fats, high-boiling amines, and solid ketones. Devise a simple scheme for isolating the ketone components.

16. How could you differentiate between: (*a*) CH_2CH_2 and CH_3OCH_3, (*b*) $CH_3COCOOH$ and CH_3CH_2COOH, (*c*) $(CH_3)_2COHCOH(CH_3)_2$ and $(C_2H_5)_2COHCOH(C_2H_5)_2$?

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Chapter 11

DIBASIC ACIDS: POLYMERIZATION

Acids which have two replaceable hydrogen atoms are called dibasic acids. An homologous series of dibasic acids starts with **oxalic acid** $(COOH)_2$, and may be represented by the general formula $(CH_2)_n(COOH)_2$. The first nine members are listed in the table below.

DIBASIC ACIDS

Name	*Formula*	*Melting Point*	*Solubility Grams per 100 Grams of Water at 20°*
Oxalic	$(COOH)_2$	189°*	8.7
Malonic	$HOOCCH_2COOH$	136°	74
Succinic	$HOOCCH_2CH_2COOH$	181°	6
Glutaric	$HOOCCH_2CH_2CH_2COOH$	98°	64
Adipic	$HOOC(CH_2)_4COOH$	153°	2
Pimelic	$HOOC(CH_2)_5COOH$	105°	5
Suberic	$HOOC(CH_2)_6COOH$	144°	0.2
Azelaic	$HOOC(CH_2)_7COOH$	106°	0.3
Sebacic	$HOOC(CH_2)_8COOH$	134°	0.1

* Anhydrous acid; the hydrate loses its water at about 100°.

General Properties. All these acids form *two types of salts*, neutral salts and acid salts; thus potassium oxalate, $(COOK)_2$ and acid potassium oxalate, HOOCCOOK. It will be noticed that, unlike most of the simple compounds hitherto studied, these substances are solids. As would be expected from the predominance of the carboxyl groups, the lower members are soluble in water.

The melting points and solubility in water show an alternation as we proceed up the series. This is shown by the values in the table and in Fig. 10. The acids with an even number of carbon atoms are higher melting and have a lower solubility; with increase in molecular weight the melting point decreases. The melting points of the acids with an odd number of atoms at first decrease and then increase. The

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two series finally appear to converge. This complex relationship is different from the regular and gradual increase in boiling points so often noted in other series. As a general rule, the melting points of organic compounds do not show the same regular change in an homologous series as do the boiling points.

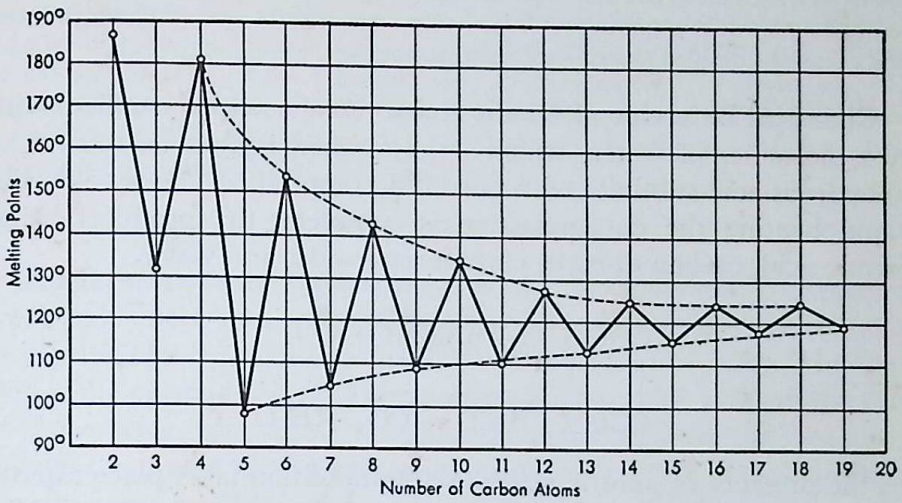

FIG. 10. The melting points of the dibasic acids, $(CH_2)_n(COOH)_2$.

OXALIC ACID

Preparation of Sodium Oxalate. The first member of the series occurs in many plants, usually as the acid potassium salt. Thus, both rhubarb and sorrel contain considerable quantities of oxalates. The acid has been an article of commerce for many years. Its sodium salt was formerly prepared by fusing sawdust with a mixture of sodium and potassium hydroxides and leaching the sodium oxalate from the partially charred mass. Evaporation of the solution yielded sodium oxalate. The modern method consists in heating sodium formate to 200°; at this temperature hydrogen is evolved.

$$2HCOONa \xrightarrow{200^\circ} (COONa)_2 + H_2$$

Since sodium formate is prepared from sodium hydroxide and carbon monoxide (p. 84), the modern industrial synthesis of sodium oxalate is essentially *a synthesis from coal and sodium hydroxide.*

Preparation of Soluble Nonvolatile Acids from Salts. To obtain the free acid from the sodium salt, it is necessary to proceed in a special manner which we have not hitherto encountered. Oxalic acid cannot be distilled without decomposition; it

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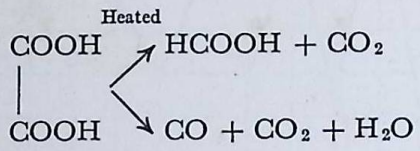
is soluble in water and insoluble in such solvents as ether and chloroform. Because of these physical properties the usual methods of obtaining an acid from its salts cannot be employed (p. 75). Therefore, the calcium salt is prepared by adding lime to an aqueous solution of sodium oxalate. Calcium oxalate is insoluble and precipitates. The precipitate is filtered and treated with the calculated quantity of dilute sulfuric acid. Calcium sulfate and oxalic acid are formed; the former, being insoluble, can be filtered. Oxalic acid crystallizes from the filtrate on evaporation. A similar procedure must be adopted in preparing acids from salts whenever the acid is soluble in water and cannot be distilled or extracted from the solution.

Chemical Behavior of Oxalic Acid. Oxalic acid crystallizes with two molecules of water, which it loses when heated to 100°. The anhydrous acid sublimes with partial decomposition above 150°. On rapid heating the decomposition is complete, the products being formic acid, carbon dioxide, carbon monoxide, and water.



In the presence of sulfuric acid the decomposition takes place rapidly when the mixture is slightly warmed; carbon monoxide, carbon dioxide, and water are the products.

Oxalic acid, like formic acid, is easily oxidized to carbon dioxide and water. In acid solution potassium permanganate is reduced to manganous salts by oxalates.

$$5(COOH)_2 + 2KMnO_4 + 3H_2SO_4 \longrightarrow K_2SO_4 + 2MnSO_4 + 10CO_2 + 8H_2O$$

This reaction is often used in quantitative analysis. Large quantities of oxalic acid and its salts are used in laundry work for removing iron stains and ink spots. Oxalic acid is oxidized by the ferric compounds, and they in turn are reduced to the more soluble ferrous salts.

The characteristic reactions of the fatty acid series are also typical of the dibasic acids. Thus, oxalic acid when treated with phosphorus pentachloride forms the acid chloride, **oxalyl chloride,** ClCOCOCl. When heated with an alcohol, first one carboxyl group and then the other is esterified. The compounds which have one unesterified carboxyl group are usually designated as *acid esters;* those in which the esterification is complete, *neutral esters.* Since the latter are the most common representatives of the esters of dibasic acids, they are usually named without any prefix to indicate the number of ester groups. Thus

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ethyl oxalate is $C_2H_5OOCCOOC_2H_5$, the neutral ester.

$$(COOH)_2 \xrightarrow{ROH} \begin{matrix} COOR \\ | \\ COOH \end{matrix} \xrightarrow{ROH} \begin{matrix} COOR \\ | \\ COOR \end{matrix}$$

Oxalic acid is a surprisingly strong acid; the value of K_A is 9×10^{-2}. Its position in the diagram shown on p. 77 would be just above dichloroacetic acid. The next member of the series, malonic acid, is much weaker, $K_A = 1.6 \times 10^{-3}$ (the position of chloroacetic acid on the diagram); the higher members of the series are only slightly stronger than acetic acid. (Succinic acid, $K_A = 6.9 \times 10^{-5}$, glutaric acid, $K_A = 5.3 \times 10^{-5}$, adipic, $K_A = 4.2 \times 10^{-5}$, pimelic, $K_A = 3.4 \times 10^{-5}$, as compared with acetic acid, $K_A = 1.86 \times 10^{-5}$.)

MALONIC ACID

Preparation from Chloroacetic Acid. Malonic acid is prepared from acetic acid by a series of reactions which illustrates several general principles in regard to the synthesis of complex acids. The first step is the preparation of **chloroacetic acid** (p. 100). The sodium salt of chloroacetic acid reacts with sodium cyanide exactly like an alkyl halide; the product is the sodium salt of the half nitrile of malonic acid (**cyanoacetic acid**).

$$CH_2ClCOONa + NaCN \longrightarrow CH_2\begin{matrix} CN \\ \diagup \\ \diagdown \\ COONa \end{matrix} + NaCl$$

This nitrile on hydrolysis yields malonic acid.

$$CH_2\begin{matrix} CN \\ \diagup \\ \diagdown \\ COOH \end{matrix} + 2H_2O + HCl \longrightarrow CH_2\begin{matrix} COOH \\ \diagup \\ \diagdown \\ COOH \end{matrix} + NH_4Cl$$

Loss of Carbon Dioxide on Heating. Like oxalic acid, malonic acid loses carbon dioxide on heating; the other product is acetic acid.

$$CH_2(COOH)_2 \xrightarrow{150^\circ} CH_3COOH + CO_2$$

The simple fatty acids and the higher members of the dibasic acid series do not decompose in this way on heating. As a rule the carboxyl group is a stable arrangement of atoms and does not undergo a change even at 200°. The presence of certain kinds of atoms or groups on the carbon atom holding the carboxyl group, however, alters this situation.

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Three halogen atoms have much the same influence as an additional carboxyl group; trichloroacetic acid, CCl_3COOH, loses carbon dioxide rapidly on boiling its water solution.

$$CCl_3COOH \longrightarrow CHCl_3 + CO_2$$

The changes in structure which result in some acids losing carbon dioxide rapidly at relatively low temperatures are changes which affect the *rate* of the reaction and not the equilibrium. As a matter of fact, if a suitable catalyst could be found acetic acid would decompose to methane and carbon dioxide as completely as malonic acid decomposes to acetic acid and carbon dioxide. Accurate calculations of the equilibrium constants from thermal data show that with both acetic acid and malonic acid the equilibrium mixtures at 25° and 1 atm would contain no measurable amount of acid.

The hypothetical reaction between methane and carbon dioxide is slightly exothermic. Since it is of the type $A + B \rightarrow AB$ ($RH + CO_2 \rightarrow RCOOH$) it is not surprising that, according to our rule (p. 170), the equilibrium constant corresponds to a mixture in which the factors predominate over the product. At 25°, the concentration of acetic acid vapor in equilibrium with the two gases would be only 10^{-6} that of the reactants.

Malonic Esters. The esters of malonic acid, e.g., **ethyl malonate,** $CH_2(COOC_2H_5)_2$, are extensively used in the synthesis of compounds in the laboratory. A consideration of such syntheses involves, however, a discussion of the peculiar properties of these and other esters and will be postponed until Chap. 14. Malonic esters are prepared directly from cyanoacetic acid by boiling it with alcohol and acid.

$$CH_2\begin{matrix}CN\\COOH\end{matrix} + 2C_2H_5OH + H_2SO_4 \longrightarrow CH_2(COOC_2H_5)_2 + NH_4HSO_4$$

THE HIGHER DIBASIC ACIDS

Oxalic acid and malonic acid differ from the other members of the dibasic acid series in some of their reactions and in their method of preparation. The other members of the series have similar chemical properties and may be all prepared by the same general methods.

General Methods of Preparation. The dibasic acids may be prepared by oxidizing the corresponding glycols according to the following general equation.

$$(CH_2)_n\begin{matrix}CH_2OH\\CH_2OH\end{matrix} + 4[O] \longrightarrow (CH_2)_n\begin{matrix}COOH\\COOH\end{matrix} + 2H_2O$$

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The dibasic acids are conveniently prepared from the glycols with *two less* carbon atoms by the preparation of the dibromide, the dinitrile, and hydrolysis. This method is illustrated by the synthesis of succinic acid from ethylene glycol.

$$\begin{array}{c} CH_2OH \\ | \\ CH_2OH \end{array} \xrightarrow{HBr} \begin{array}{c} CH_2Br \\ | \\ CH_2Br \end{array} \xrightarrow{NaCN} \begin{array}{c} CH_2CN \\ | \\ CH_2CN \end{array} \xrightarrow[H_2O]{HCl} \begin{array}{c} CH_2COOH \\ | \\ CH_2COOH \end{array}$$

The Grignard method of preparing acids from the corresponding halides can be used for preparing dibasic acids. The dihalides above trimethylene bromide react with magnesium in absolute ether to form dimagnesium derivatives which combine with 2 moles of carbon dioxide. When this sequence of reactions is applied to 1,5-dibromopentane, a 50 per cent yield of pimelic acid is obtained.

The electrolysis of the acid esters of the dibasic acids provides a method of nearly doubling the length of the chain. By this method a number of dibasic acids of very high molecular weight have been prepared; the yields are often rather poor, however. As an example, the preparation of adipic ester from the acid ester of succinic acid may be given.

$$2\begin{array}{c} CH_2COOC_2H_5 \\ | \\ CH_2COO^- \end{array} \xrightarrow[\text{anode}]{\text{At the}} \underbrace{\begin{array}{c} CH_2COOC_2H_5 \\ | \\ (CH_2)_2 \\ | \\ CH_2COOC_2H_5 \end{array}}_{\text{Ethyl ester of adipic acid}} + 2CO_2 + 2 \text{ electrons}$$

Succinic Acid. This is the only one of the higher dibasic acids which is a commonly occurring substance. It occurs in amber (a fossil gum) and was originally prepared by the distillation of this material. It has been isolated from a variety of plants, certain animal tissue, and the urine of animals. It plays an important part in the oxidation reactions in living cells (Chap. 20). It is prepared industrially by the electrolytic reduction of fumaric acid (p. 314).

$$\underbrace{HOOCCH = CHCOOH}_{\text{Fumaric acid}} + 2[H] \longrightarrow HOOCCH_2CH_2COOH$$

CYCLIC ANHYDRIDES

Succinic acid and glutaric acid differ from all the other members of the series $(CH_2)_n(COOH)_2$ by the fact that they readily form *cyclic anhydrides*. This may be illustrated by the preparation of succinic anhydride.

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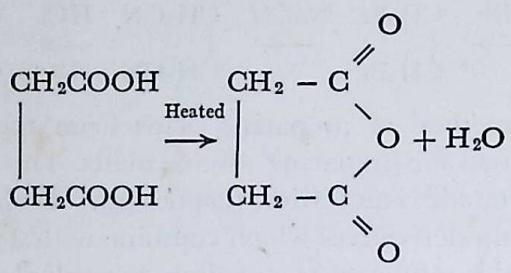
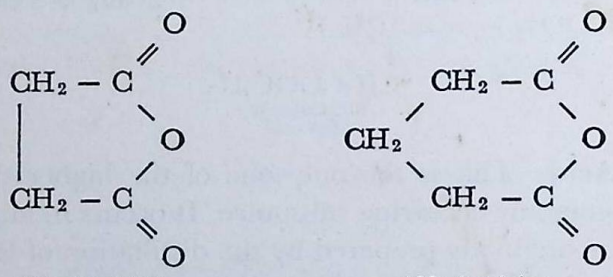
Succinic Anhydride. Succinic anhydride, $(CH_2CO)_2O$, is a white, crystalline solid (mp 120°) obtained by heating succinic acid alone or with dehydrating agents such as acetic anhydride or phosphorus oxychloride ($POCl_3$).



This anhydride differs from acetic anhydride in that the two acyl groups are part of the same molecule. Obviously such cyclic anhydrides can be formed only from polybasic acids.

Dehydration of Dibasic Acids. The peculiar behavior of succinic and glutaric acids is connected with the fact that the ring in their anhydrides contains five and six atoms. In general we shall find that compounds containing five- and six-membered rings are usually more easily prepared than those with larger or smaller ring systems.



5-Membered ring; succinic anhydride

6-Membered ring; glutaric anhydride

The two lower members of the dibasic acid series have their own peculiarities on dehydration. The behavior of oxalic acid has been discussed; malonic acid on heating with phosphorus pentoxide yields a gas, *carbon suboxide*, O = C = C = C = O, which belongs to the group of ketenes (p. 323). Adipic and the higher acids do not lose water when they are heated by themselves; but, when they are heated with acetic anhydride or phosphorus oxychloride, they do yield anhydrides of high molecular weight. These latter named anhydrides are the result of anhydride formation between two carboxyl groups of different molecules and the structure of the anhydrides

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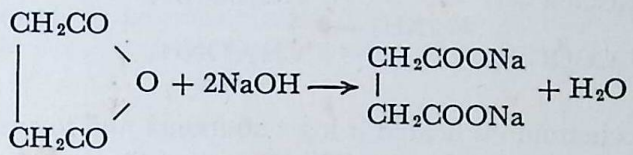
may be represented by the following formula for polyadipic anhydride.

$$-(CH_2)_4\overset{\overset{O}{\|}}{C}-O-\overset{\overset{O}{\|}}{C}-(CH_2)_4\overset{\overset{O}{\|}}{C}-O-\overset{\overset{O}{\|}}{C}-(CH_2)_4\overset{\overset{O}{\|}}{C}-O-\overset{\overset{O}{\|}}{C}-(CH_2)_4-$$

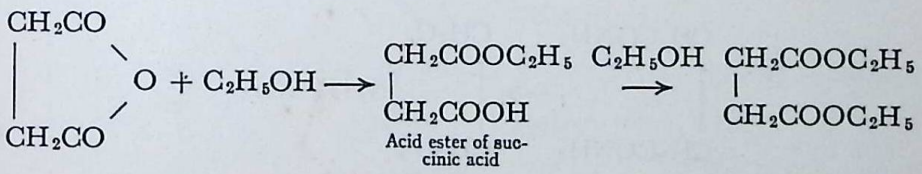
Molecular weight may be greater than 5000

When heated in a very high vacuum the anhydrides of high molecular weight yield cyclic anhydrides which, on treatment with small amounts of acids as catalysts, revert to the anhydrides of high molecular weight. These cyclic anhydrides, both in their mode of formation and their ready conversion to high molecular weight anhydrides, are very different from succinic and glutaric anhydrides.

Reactions of Cyclic Anhydrides. In their reactions the cyclic anhydrides closely resemble the simple acid anhydrides. They are hydrolyzed by water with the formation of the corresponding acid; alkali is usually needed to catalyze this reaction and sometimes to complete it.



With alcohol an acid ester is formed which on further boiling with alcohol yields the neutral ester.



Acid ester of succinic acid

AMIDES OF DIBASIC ACIDS

The general method of preparation of the amides of the dibasic acids follows the reactions outlined in connection with a consideration of the amides of the fatty acids. Succinic acid and glutaric acid occupy an exceptional place, as here cyclic compounds known as *cyclic imides* may be formed.

Oxamide and Oxamic Acid. The diamide of oxalic acid, oxamide, $(CONH_2)_2$, is a white crystalline powder, insoluble in water and alcohol. On heating, it sublimes with partial decomposition. It can

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be formed by the action of ammonia on ethyl oxalate or by heating ammonium oxalate.

$$\begin{array}{l} COOC_2H_5 \\ | \\ COOC_2H_5 \end{array} + 2NH_3 \longrightarrow \underset{\text{Oxamide}}{\begin{array}{l} CONH_2 \\ | \\ CONH_2 \end{array}} + 2C_2H_5OH$$

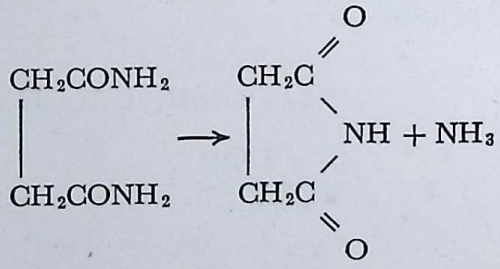
The acid amide of oxalic acid, $HOOCCONH_2$, is known as *oxamic acid*. It is both an amide and an acid. It is prepared by heating ammonium acid oxalate.

$$\begin{array}{l} COOH \\ | \\ COONH_4 \end{array} \longrightarrow \underset{\text{Oxamic acid}}{\begin{array}{l} COOH \\ | \\ CONH_2 \end{array}}$$

Succinamide and Succinimide. The diamide of succinic acid, $(CH_2)_2(CONH_2)_2$, is a crystalline solid which is formed by the action of ammonia on ethyl succinate.

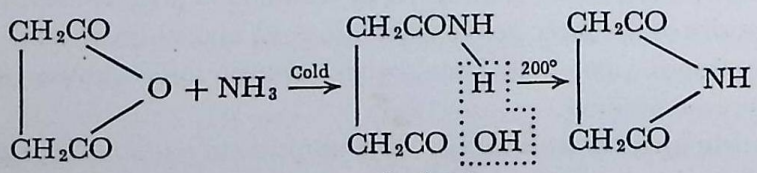
$$\begin{array}{l} CH_2COOC_2H_5 \\ | \\ CH_2COOC_2H_5 \end{array} + 2NH_3 \longrightarrow \underset{\text{Succinamide}}{\begin{array}{l} CH_2CONH_2 \\ | \\ CH_2CONH_2 \end{array}} + 2C_2H_5OH$$

When succinamide is heated it loses ammonia and forms the cyclic compound known as *succinimide*. This is a crystalline solid, melting at 126° and readily soluble in water.



Succinimide

Succinimide may also be formed from succinic anhydride and ammonia.



Succinamic acid

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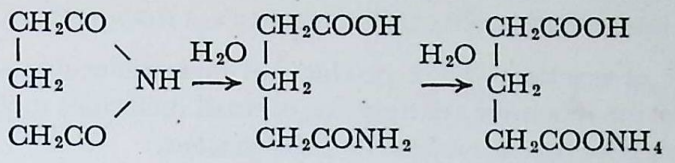
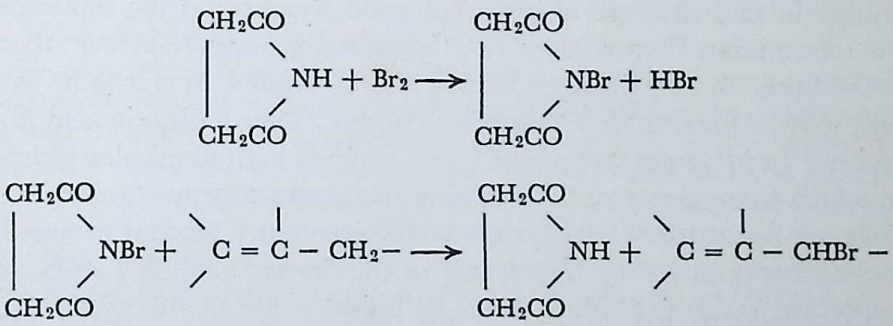
The isolation of the intermediate (succinamic acid) is not necessary if the reaction is carried out at high temperatures. **Glutarimide** is prepared in a manner similar to succinimide.

The cyclic imides on boiling with aqueous acids or bases are hydrolyzed with the formation of the acid and ammonia. The first product of the hydrolysis is the acid amide which can be isolated under suitable conditions.



The presence of two acyl groups on the nitrogen atom of succinimide makes the hydrogen atom more acidic than in a simple amide. Although the compound is neutral in water solutions, it will readily form a sodium or potassium salt. Such salts of the cyclic imides are somewhat hydrolyzed by water but not decomposed by alcohol (except slowly as the alcohol causes the opening of the ring).

Succinimide can be brominated to form the N-bromo derivative which is a useful reagent for brominating certain types of unsaturated compounds.



Esters and Amides of High Molecular Weight. The esterification of dibasic acids with glycols yields an interesting group of compounds analogous to the high-molecular-weight anhydrides considered on page 226. In the esterification, unlike molecules (acid and alcohol) interact to form a long-chain molecule; depending on the catalyst, temperature, and time, substances with different average molecular weights are formed. A similar reaction takes place between diamines and dibasic acids; the products are amides of high molecular weight. These reactions have been studied with a variety of dibasic acids, glycols, and diamines. The structures of the products may be repre-

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sented by the following general formulas:

$$\cdots OCH_2(CH_2)_xCH_2OC\overset{\overset{\displaystyle O}{\|}}{(CH_2)_y}C\overset{\overset{\displaystyle O}{\|}}{O}CH_2(CH_2)_xCH_2OC\overset{\overset{\displaystyle O}{\|}}{(CH_2)_y}C\overset{\overset{\displaystyle O}{\|}}{\cdots}$$

Polyester formed from $HOCH_2(CH_2)_xCH_2OH$ and $HOOC(CH_2)_yCOOH$

$$\cdots NHCH_2(CH_2)_xCH_2NHC\overset{\overset{\displaystyle O}{\|}}{(CH_2)_y}C\overset{\overset{\displaystyle O}{\|}}{N}HCH_2(CH_2)_xCH_2NHC\overset{\overset{\displaystyle O}{\|}}{(CH_2)_y}C\overset{\overset{\displaystyle O}{\|}}{\cdots}$$

Polyamide formed from $NH_2CH_2(CH_2)_xCH_2NH_2$ and $HOOC(CH_2)_yCOOH$

This type of reaction, where products of high molecular weight are formed by the repetitive splitting out of small molecules such as water or alcohol, is known as *condensation polymerization.*

The interaction of polyfunctional molecules proceeds in a fashion similar to the interaction of monofunctional molecules. The only peculiarities arise when the two groups in the same molecule can react with each other because of their nearness in space, as in the formation of the cyclic anhydrides. If there are just two functional groups in each molecule, then long-chain compounds of high molecular weight are the normal products. These are related to natural and synthetic rubber in that they are of high molecular weight and the molecules are long chains. If more than two functional groups are present then, in addition to the linkages joining the molecules in a chain, *cross links* may be formed, as in vulcanized rubber. Thus a dibasic acid and glycerol (a *trihydroxy* compound) give esters of high molecular weight in which there are cross links joining the chains together; these cross links are formed by esterification of the secondary alcohol groups in two different chains by a molecule of the dibasic acid. A number of important resins extensively used in industry are of this type; they are considered later together with some other artificial resins (p. 513).

Nylon. A synthetic fiber, Nylon, is prepared industrially by the interaction of adipic acid and hexamethylene diamine. The resulting polyamide of high molecular weight (10,000 to 25,000) melts at about 260° and the molten material can be drawn into fine threads. These threads can be stretched to four times their length at room temperature, and, unlike elastic material, they do not contract when the tension is released. This process of "cold drawing" changes an essentially amorphous material into a fibrous one; the fiber has high tensile strength and luster and resembles silk in many ways.

The adipic acid required for this large industry is obtained by the oxidation of a cyclic ketone, cyclohexanone, which in turn is

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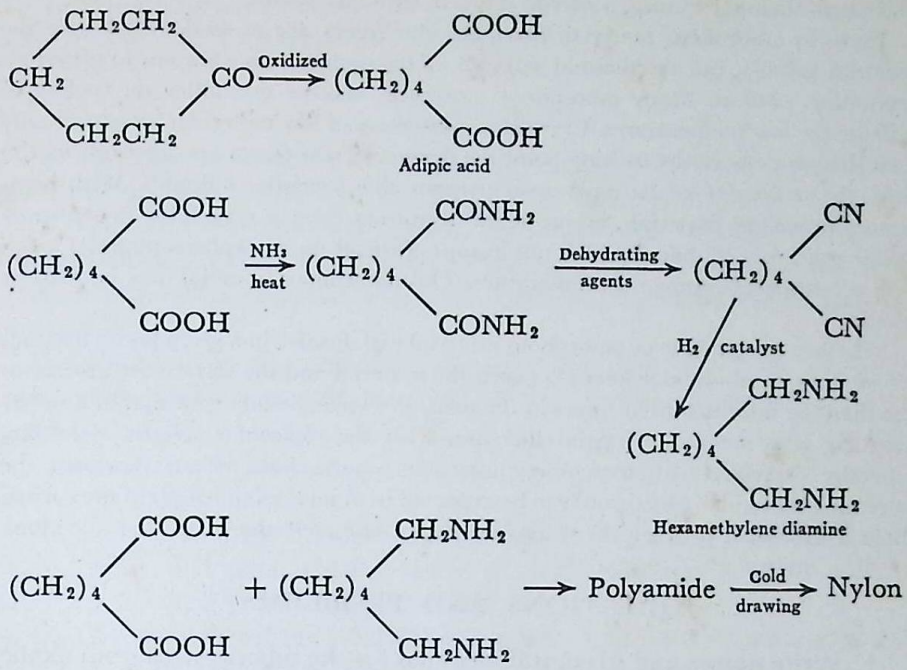
prepared from phenol (p. 429). The diamine is prepared from the acid by way of the amide and the nitrile.



Cohesive Forces between Large Molecules. The interesting and important change which the polyamides of high molecular weight undergo when "cold drawn" as fibers is the result of a change in the intermolecular pattern. Before stretching, the material is amorphous; the long molecules are probably curled up and in a random orientation. The process of drawing apparently uncurls a number of the long-chain molecules and places them in a definite orientation; the intermolecular forces (van der Waals' forces, p. 71) are then sufficient to keep this pattern after the tension has been released. A study of the drawn fiber by X rays shows that the fiber partakes of the nature of a crystalline substance, showing a definite and characteristic X-ray pattern; the amorphous material does not. Natural fibers such as silk and wool (proteins, Chap. 19) and cotton (cellulose, Chap. 15) likewise have definite X-ray patterns. Rubber on stretching takes on the nature of a crystalline arrangement as shown by X rays, but reverts to the amorphous condition on releasing the tension. The difference in this respect between the polyisoprene (rubber) and the polyamide (Nylon) is probably connected with the fact that one is a hydrocarbon and the other an amide. The intermolecular forces between hydrocarbons are less than between compounds containing oxygen and nitrogen which are more polar in character; compare the boiling points of hydrocarbons and amides of the same molecular weight. The intermolecular forces in rubber are not sufficient to keep the long chains oriented in a definite arrangement side by side.

Fibers of course are not crystals in the sense that simple organic molecules of low molecular weight are crystals. In fibers patches of crystalline material are connected by amorphous material in which the intermolecular forces hold a few molecules in a

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crystal unit, and still weaker forces hold crystal units together; in a fiber the same forces are at work as in small molecules, but, because of the large size of the molecules and their chainlike nature, a special physical structure results.

Even in amorphous material intermolecular forces are at work which give the material solidity, but the thermal agitation of the molecules is sufficient to prevent a crystalline pattern. Many amorphous substances become crystalline on cooling to sufficiently low temperatures. Crystals of substances of low molecular weight usually melt sharply; above the melting point the intermolecular forces are only sufficient to hold the molecules in the loose arrangements characteristic of liquids. With high-molecular-weight materials, however, the transition from a crystalline or semicrystalline solid to a mobile liquid is not abrupt. Instead an amorphous material exists over a considerable range of temperature. This amorphous material may be hard or plastic.

Whether a crystalline or amorphous material will dissolve in a given liquid depends on whether the molecular forces between the material and the solvent are greater or less than the intermolecular forces in the solid. We have already seen that in a rather irregular way the melting point increases with the molecular weight. Solubility generally decreases with increasing molecular weight. Both effects represent the increasing molecular cohesiveness to be expected with increasing length of the carbon chain if the forces between the chains were approximately the same atom for atom.

QUESTIONS AND PROBLEMS

1. Write names and structural formulas for the dibasic acids from oxalic through adipic acid.

2. Outline procedures for obtaining propionic acid and oxalic acid from sodium propionate and sodium oxalate, respectively. Give the reasons why different procedures are necessary.

3. Predict the behavior of each of the following acids when it is dissolved in excess ethyl alcohol containing a small amount of sulfuric acid and the solution is heated for two hours at 80°: (*a*) $(C_2H_5)_2CCOOH$, $\mid$ CH_2COOH (*b*) $CH_3CH_2CH_2CH(CH_2COOH)_2$, and (*c*) $(CH_3)_2CCOOH$, $\mid$ $(CH_3)_2CCOOH$. Give the reasoning on which you made your predictions.

4. Outline the steps in the synthesis of (*a*) adipic acid and (*b*) tetramethylene glycol from ethylene.

5. Write balanced equations for the following reactions: (*a*) oxalyl chloride and methyl alcohol, (*b*) succinic anhydride and ethyl alcohol, (*c*) acetic anhydride and ethylene glycol, (*d*) ethyl oxalate and ammonia,

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(*e*) glutaric anhydride and ammonia, (*f*) succinimide and ethyl alcohol.

6. Outline the steps in the manufacture of Nylon from cyclohexanone.

7. What tests would you use to tell whether a sample of an unknown acid was $CH_3CH_2CH(COOH)_2$ or $CH_3CHCOOH$?

$$\begin{array}{l} \quad\;\; | \\ CH_2COOH \end{array}$$

8. Describe the reactions that take place between dibasic acids and either glycols or diamines. What are the structures of the products formed?

9. Outline the syntheses of malonic ester from ethyl alcohol, oxalic acid from the elements, glutaric acid from glycerol, and oxamide from oxalic acid.

10. Compare the behavior of malonic acid, glutaric acid, and adipic acid on heating.

11. Write balanced equations for the reactions: (*a*) formic acid, potassium dichromate, and dilute sulfuric acid; (*b*) oxalic acid, potassium permanganate, and dilute hydrochloric acid; (*c*) trichloroacetic acid, heated; (*d*) succinic anhydride and dimethylamine; (*e*) cyanoacetic acid, methyl alcohol, and sulfuric acid.

12. Outline the best method for each of the conversions: (*a*) succinic acid to the acid ethyl ester, (*b*) the latter to adipic ester, (*c*) succinic acid to succinimide, (*d*) glycerol to glutaric acid.

13. Given a chloroform solution of succinic acid, butyric acid, and glutaric anhydride, devise a scheme for separating this mixture.

14. Show how you could differentiate between: (*a*) $CH_2(COOC_2H_5)_2$ and $CH_3(CH_2)_3COOC_2H_5$, (*b*) $CH_3COCOOC_2H_5$ and $C_2H_5OCOCOOC_2H_5$, (*c*) $\begin{array}{l} CH_2CO \\ | \quad\;\; \diagdown \\ | \quad\;\; \diagup O \\ CH_2CO \end{array}$ and $(CH_3CH_2CO)_2O$, (*d*) $CH_3CH_2CONH_2$ and $\begin{array}{l} CH_2CONH_2 \\ | \\ CH_2CONH_2 \end{array}$.

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Chapter 12

HYDROXY ACIDS, ALDEHYDES, AND KETONES

One or more hydrogen atoms of the fatty acids or of the dibasic acids may be replaced by hydroxyl groups. The resulting compounds are known as *hydroxy acids*. They are both acids and alcohols and in general have the reactions of both classes of compounds. A number are of commercial importance and of interest to the biochemist as they occur in plants and animals. It will be recalled that there is no method for directly substituting a hydrogen atom of a paraffin hydrocarbon by an hydroxyl group. Similarly we find that the hydroxy acids cannot be prepared directly from the fatty acids. The preparation of the hydroxy acids usually proceeds from the corresponding halogen compounds—chloro or bromo acids. We shall, therefore, first consider these classes of substances (which are of minor importance by themselves), and then turn to the hydroxy acids which may be prepared from them.

HALOGEN-SUBSTITUTED ACIDS

Classification and Nomenclature. The methods of preparation and reactions of the acids containing a halogen atom differ according to the position of the atom. It is usual to indicate the position of an atom or group in a substituted fatty acid by means of a Greek letter. The lettering starts with the *carbon atom next to the carboxyl group*. The method is illustrated by the following examples:

$\underset{\gamma}{CH_3}\underset{\beta}{CH_2}\underset{\alpha}{CHCl}COOH$	α-chlorobutyric acid
$\underset{\gamma}{CH_2Br}\underset{\beta}{CH_2}\underset{\alpha}{CH_2}COOH$	γ-bromobutyric acid
$CH_3CHBrCHBrCOOH$	α,β-dibromobutyric acid

It is common practice to designate the two carbon atoms next to the two carboxyl groups in dibasic acids as α and α' and continue the lettering in the two directions until they meet. Thus,

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$HOOCCBr_2CH_2COOH$ is α,α-dibromosuccinic acid, while α,α'-dibromosuccinic acid is $HOOCCHBrCHBrCOOH$.

Preparation of Bromo and Chloro Acids. The preparation of alpha halogen acids from the fatty acids has already been considered (p. 99). Beta halogen acids may often be prepared by the addition of halogen acids to unsaturated acids, while α,β-dibromo or dichloro (but not diiodo) acids are formed by the addition of bromine or chlorine to the same acid. The behavior of acrylic acid (p. 308) will suffice as an example.

$$\underset{\text{Acrylic acid}}{CH_2 = CHCOOH} \xrightarrow{HBr} CH_2BrCH_2COOH$$

$$CH_2 = CHCOOH \xrightarrow{Br_2} CH_2BrCHBrCOOH$$

It should be noted that the halogen atom always goes to the beta position when acids containing the linkage $C = C - COOH$ react with halogen acids (see further, p. 320).

Acids containing halogen in the beta or gamma position may also be prepared from the glycols, which in turn may be synthesized by a variety of methods (p. 203). The preparation of β-chloropropionic acid from trimethylene glycol is an illustration of this method.

$$CH_2OHCH_2CH_2OH \xrightarrow{HCl} CH_2ClCH_2CH_2OH \xrightarrow[HNO_3]{[O]} CH_2ClCH_2COOH$$

Beta halogen acids readily lose a molecule of halogen acid, forming the unsaturated acid. As this reaction is more rapid than most metathetical processes, it is difficult to replace the halogen atom in the beta position by other atoms or groups.

Halogen acids having the substituent atom on the end of the chain are sometimes known as *omega* (ω) *halogen acids*. They may be prepared from the corresponding chloro or bromohydrins.

Physical Properties. The physical properties of some of the simpler halogen substitution products of the fatty acids are given in the accompanying table. The alpha halogen acids and their esters have a marked physiological action. The esters of the alpha-substituted acids are lachrymatory substances like the halogenated aldehydes and ketones. **Trichloroacetic acid** is used in medicine as a corrosive agent for removing the outer tissues as required in the treatment of corns and warts. (It is manufactured by the cautious oxidation of chloral.)

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PHYSICAL PROPERTIES OF SOME CHLORO-, BROMO-, AND IODO-ACIDS AND ESTERS

Name	*Formula*	*Melting Point*	*Boiling Point*
Chloroacetic acid	$CH_2ClCOOH$	62°	189°
Bromoacetic acid	$CH_2BrCOOH$	50°	208°
Iodoacetic acid	CH_2ICOOH	83°	
Dichloroacetic acid	$CHCl_2COOH$	11°	194°
Trichloroacetic acid	CCl_3COOH	55°	200°
α-Chloropropionic acid	$CH_3CHClCOOH$		186°
β-Chloropropionic acid	CH_2ClCH_2COOH	41°	204°
Halo esters			
Ethyl chloroacetate	$CH_2ClCOOC_2H_5$		144°
Ethyl dichloroacetate	$CHCl_2COOC_2H_5$		158°
Ethyl trichloroacetate	$CCl_3COOC_2H_5$		168°

The influence of a halogen atom in the alpha position on the strength of the acid is very marked. Trichloroacetic acid is nearly as strong as hydrochloric acid in water solution. The mono- and dichloroacetic acids are not so strong (see Fig. 4, p. 77).

If the halogen atom is removed from the carboxyl group by one or more atoms the effect on the dissociation constant is very slight.

Reactions of Alpha Halogen Acids. A halogen atom in the alpha position to a carboxyl group is readily replaced by a variety of groups. In general, the rate of such metathetical reactions is considerably more rapid than with the alkyl halides themselves. The esters of the alpha halogen acids enter into exactly the same type of metathetical reactions. The following reactions of α-bromopropionic acid will illustrate the common and useful reactions.

1. *Preparation of hydroxy acid.*

$$CH_3CHBrCOOH \xrightarrow[\text{or KOH}]{\text{AgOH}} CH_3CHOHCOOH$$

2. *Preparation of amino acid.*

$$CH_3CHBrCOOH \xrightarrow{NH_3} CH_3CHNH_2COOH$$

3. *Preparation of cyano acid* (half nitrile of a substituted malonic acid).

$$CH_3CHBrCOOH + KCN \longrightarrow CH_3CHCNCOOH + KBr$$

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A Grignard reagent cannot be prepared from a halogen-substituted acid or ester whether the halogen be in the alpha or any other position. The *alpha bromo esters*, however, form **organozinc** compounds similar to the Grignard reagents. These compounds will add to the carbonyl group of an aldehyde or ketone, but will not add to esters. The process, which is known as the **Reformatsky reaction,** may be illustrated by the following example.

$$BrCH_2COOC_2H_5 + Zn \longrightarrow BrZnCH_2COOC_2H_5$$

$$(CH_3)_2CO + BrZnCH_2COOC_2H_5 \longrightarrow (CH_3)_2C(OZnBr) - CH_2COOC_2H_5$$

$$(CH_3)_2C(OZnBr) - CH_2COOC_2H_5 \xrightarrow{H_2O} (CH_3)_2C(OH)CH_2COOC_2H_5$$

HYDROXY ACIDS

The important hydroxy acids which occur in nature are listed in the table which follows.

SOME IMPORTANT HYDROXY ACIDS

Name	*Formula*	*Occurrence*
Malic acid	CHOHCOOH | CH_2COOH	Unripe fruits, gooseberries, rhubarb stalks, unripe grapes, cherries, tomatoes
Lactic acid	$CH_3CHOHCOOH$	Sour milk, in muscle after activity, beet molasses, in blood and urine
Citric acid	CH_2COOH / C(OH)COOH \ CH_2COOH	All citrus fruits
Glycolic acid	$CH_2OHCOOH$	Chief acid constituent of sugar cane; present in beet juice; unripe grapes
Tartaric acid	CHOHCOOH | CHOHCOOH	Argol (in wine casks) (monopotassium salt)
β-Hydroxybutyric acid	CH_3CHOH | CH_2COOH	Urine from those suffering with diabetes

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Nomenclature. The acids listed above, with one exception, have the hydroxyl group adjacent to a carboxyl group; they are called *alpha hydroxy acids*. The position of a hydroxyl group, like that of a halogen atom, is indicated by a Greek letter.

Synthesis. The preparation of *alpha hydroxy acids* in the laboratory is possible by two different procedures which are illustrated by the synthesis of α-hydroxypropionic acid, lactic acid.

1. We may start with the alpha chloro acid and replace the chlorine atom with hydroxyl.

$$CH_3CH_2COOH \xrightarrow{Cl_2} CH_3CHClCOOH \xrightarrow{AgOH} CH_3CHOHCOOH$$

2. We may start with an aldehyde, add hydrocyanic acid (p. 136), and then hydrolyze the hydroxy nitrile.

$$CH_3CHO + HCN \longrightarrow \underset{\text{A hydroxy nitrile or cyanohydrin}}{CH_3CHOHCN} \xrightarrow[H_2O]{HCl} CH_3CHOHCOOH$$

The *beta hydroxy acids* are prepared by the Reformatsky reaction (p. 237); the ester first formed is hydrolyzed to the acid. The beta halogen acids are not useful for the preparation of beta hydroxy acids for the reason already given on p. 235.

β-Hydroxypropionic acid, hydracrylic acid, is prepared in the following way:

$$HOCH_2CH_2Cl \xrightarrow{NaCN} HOCH_2CH_2CN \xrightarrow[NaOH]{H_2O} HOCH_2CH_2COOH$$

The *gamma hydroxy acids* can be prepared from the corresponding gamma halogen acids by replacement of halogen by hydroxyl. They may also be prepared by reduction of the corresponding keto acid.

Glycolic Acid. The simplest representative of the hydroxy acids occurs in unripe fruits. It is a crystalline solid melting at 80° and very soluble in water. It may be prepared by the action of dilute alkali on monochloroacetic acid or by merely boiling a solution of this acid with water.

$$CH_2ClCOOH + H_2O \xrightarrow{\text{Heated}} CH_2OHCOOH$$

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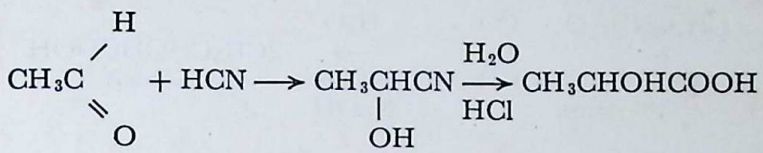
Lactic Acid. Lactic acid, $CH_3CHOHCOOH$, is formed when milk sours, according to the following reaction:

$$\underset{\text{Milk sugar}}{C_{12}H_{22}O_{11}} + H_2O \xrightarrow[\text{lactase}]{\text{Enzyme}} 4CH_3CHOHCOOH$$

For industrial purposes lactic acid is either isolated from sour milk or made by a bacterial fermentation of glucose. It is an oily liquid which is difficult to obtain pure. It is used in dyeing, and its ethyl ester is a commercial solvent.

Three isomeric lactic acids are known. One, dextro lactic acid, can be obtained from muscle; another, laevo lactic acid, can be obtained by the fermentation of lactose and certain other sugars; while the third, inactive lactic acid, results from the following synthesis.



All three lactic acids have been shown to have the same structure, that of α-hydroxypropionic acid. The explanation for their isomerism we shall discuss in the next chapter.

Lactic acid is a very important compound to the biochemist. The energy necessary for muscular action appears to be normally supplied by the decomposition of glycogen (p. 300) to lactic acid. Glycogen is a carbohydrate similar to starch; it is stored in the liver and carried by the blood stream to the muscle. A complicated series of reactions are involved in the change of glycogen to lactic acid (p. 390). Following the contraction of the muscle, the lactic acid disappears from the muscle by diffusion into the blood stream and by oxidation.

Dehydration of Hydroxy Acids. The general chemical characteristics of hydroxy acids may be said to embody the properties of both an acid and an alcohol. Thus, as acids they form salts with bases and esters with alcohols; for example, $CH_3CHOHCOONa$, is sodium lactate, and **ethyl lactate** is $CH_3CHOHCOOC_2H_5$. As alcohols, they form esters with acids; thus the acetate of lactic acid is formed from lactic acid and acetic anhydride.

$$CH_3CHOHCOOH + (CH_3CO)_2O \longrightarrow CH_3\underset{\underset{OCOCH_3}{|}}{C}HCOOH + CH_3COOH$$

It is obviously an interesting question as to whether a hydroxy acid

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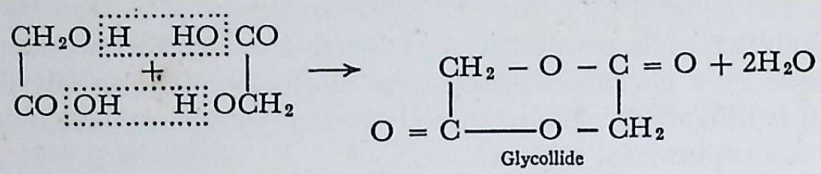
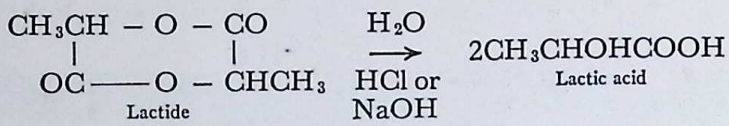
can form an ester with itself. Such a reaction does, indeed, take place when alpha hydroxy acids are treated with dehydrating agents or merely heated alone for some length of time. The reaction may be illustrated with glycollic acid, the first member of the series.

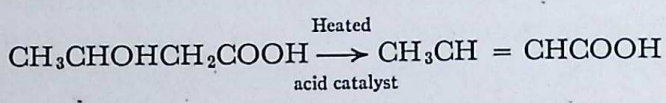


Similarly, lactic acid yields **lactide** on heating. The formation of cyclic double esters is a characteristic of alpha hydroxy acids.

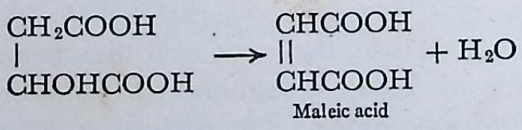
These cyclic esters on hydrolysis regenerate the hydroxy acid.

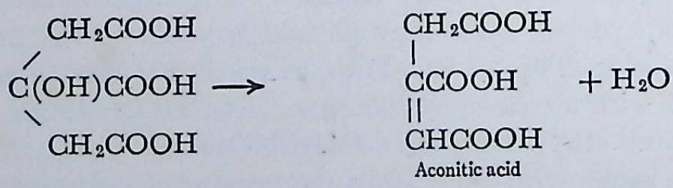


Beta hydroxy acids on heating with dehydrating agents usually lose water and form unsaturated acids.



Malic and citric acids, whose hydroxyl group is alpha to one carboxyl group and beta to another, likewise undergo dehydration to unsaturated acids.





Lactones. Gamma hydroxy acids lose water in a very interesting way, yielding cyclic esters formed from only *one* molecule of the acid. These compounds are called *lactones*. They are inner esters, and on hydrolysis yield the hydroxy acid. In the absence of base the reaction is a balanced one; in the presence of alkali the hydrolysis is complete

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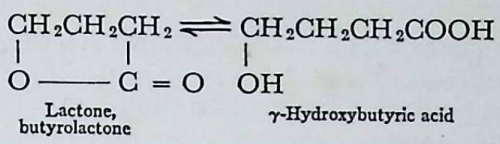
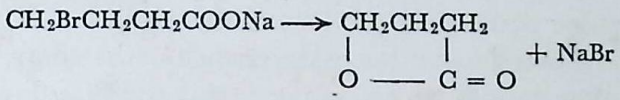
by virtue of the neutralization of the acid:



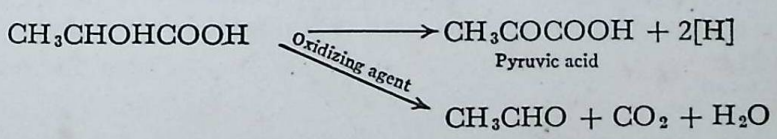
The point of equilibrium between a lactone and the hydroxy acid is often very favorable to the former, and some gamma hydroxy acids cannot be prepared. They are known only as salts or esters.

Lactones are also formed from certain delta hydroxy acids but not readily from other hydroxy acids. This fact illustrates the same general rule encountered in connection with the cyclic anhydrides—namely, the ready formation of five- or six-membered rings. Another method of preparing lactones is from chloro or bromo acids. Acids having a halogen atom in the gamma position form lactones quite rapidly when a solution of their sodium salts stands a short time. This reaction is not reversible.



Hydroxy acids under conditions of inner esterification may also form esters between two molecules, or many molecules may esterify each other in such a way that a long-chain polyester may result. The latter occurs with hydroxy acids in which the hydroxyl group is at least five carbon atoms removed from the carboxyl group. Thus, 9-hydroxynonanoic acid on heating alone or with a catalyst gives polyesters of molecular weights above 5000. If, however, an extremely dilute solution of an ω-hydroxy acid (concentration below 0.0002 molar in benzene) is dehydrated, large-ring lactones can be obtained. One very large-ring lactone has been found in nature; it is **ambrettolide,** found in certain oils, the lactone ring contains sixteen carbon atoms.

Oxidation of Alpha Hydroxy Acids. The alpha hydroxy acids are oxidized more rapidly and at a lower temperature than are secondary or primary alcohols. Acids containing the group —CHOHCOOH can undergo oxidation in aqueous solution in two different ways depending on the oxidizing agent. Thus lactic acid, or lactate ion, may be dehydrogenated to the corresponding ketonic acid (pyruvic acid), or oxidized to an aldehyde (acetaldehyde), carbon dioxide, and water.



Alpha hydroxy acids containing a tertiary hydroxyl group undergo

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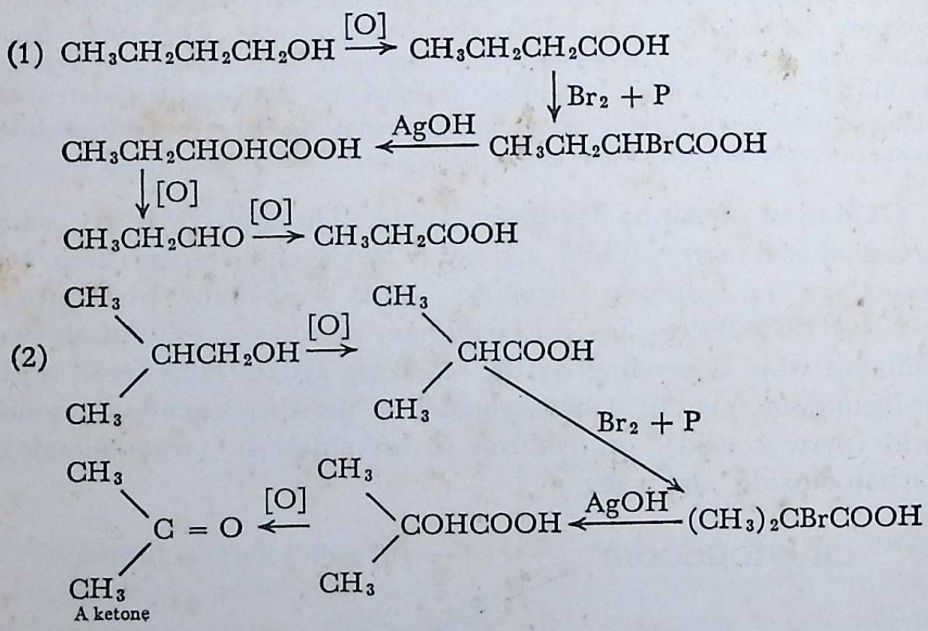
the second type of oxidation:

$$(CH_3)_2COHCOOH \xrightarrow{KMnO_4} (CH_3)_2CO + CO_2 + H_2O$$

Structure of a Carbon Chain. The elimination of carbon dioxide from alpha hydroxy acids provides a method of degrading an acid step by step. In this way it is possible to determine the structure of the carbon chain in an acid. This reaction provides one of the best methods of "going down the series," and can also be used for preparative purposes.

As a simple example of the application of this method we may use it to determine the structures of the two isomeric primary butyl alcohols. Each alcohol is oxidized to an acid which is converted to an alpha hydroxy acid through the bromo acid. The alpha hydroxy acid is oxidized, and the series of reactions is then repeated until a known acid or a ketone is the final product of the oxidation. The structure of this ketone shows the position of the branch in the chain. (If an acid is obtained that cannot be brominated, this shows a double branch in the chain at this point.)



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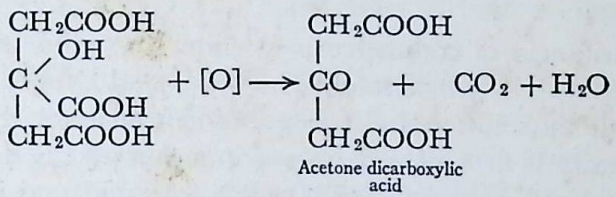
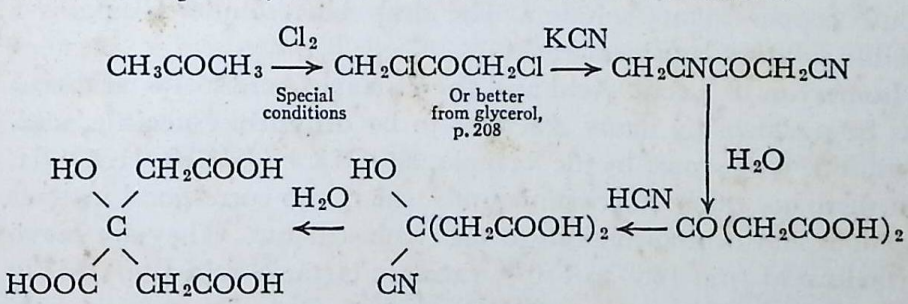
In the application of this method it is usually only necessary to remove a few carbon atoms before the product is a substance of known structure which may be identified.

Citric Acid. One of the acids most widely distributed in nature is citric acid. It occurs particularly in citrus fruits as the name indicates. It crystallizes with a molecule of water which is lost on heating. The hydrated acid melts at about 100°; the anhydrous acid at 153°. The acid is very soluble in water. It forms a variety of salts, some of which are used in pharmaceutical preparations. The acid itself is widely used in the preparation of beverages. It is prepared either from citrus fruits which are not marketable or by the fermentation of glucose by a certain mold.

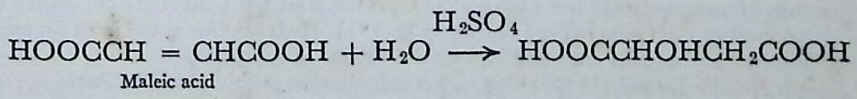
The structure of citric acid follows from its oxidation to **acetone dicarboxylic acid.**



The latter substance may be prepared from dichloroacetone (p. 208), and the complete synthesis of citric acid is thus as follows.



Malic Acid. Hydroxysuccinic acid, $HOOCCHOHCH_2COOH$, is known as *malic acid*. Like glycollic acid it occurs in unripe fruits. It may be prepared by the action of alkali on chloro- or bromosuccinic acid or by combining maleic acid (p. 313) with water by means of sulfuric acid. This last method is now used for the industrial preparation of malic acid.



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The synthetic acid melts at 130° to 131°; the acid which occurs in nature, at 100°. The two forms also differ in their action on polarized light, the former being without effect while the latter causes a rotation. The structure of both the synthetic and natural acids is established by the fact that on heating with hydrogen iodide they are reduced to succinic acid.

$$\begin{array}{l} CHOHCOOH \\ | \\ CH_2COOH \end{array} + 2HI \longrightarrow \begin{array}{l} CH_2COOH \\ | \\ CH_2COOH \end{array} + I_2 + H_2O$$

Tartaric Acid. Tartaric acid, $(CHOHCOOH)_2$, is obtained from the crude potassium acid tartrate, known as *argol*, which crystallizes in wine casks. This salt is probably present in the original wine and separates slowly. When purified by crystallization from water, it is known as *cream of tartar* and is widely used in the manufacture of baking powder.

The tartaric acid of commerce is a white, crystalline solid which melts at 168° to 170°; it is soluble in water and cannot be readily extracted from the solution. In its preparation from argol, the insoluble calcium tartrate is first formed by precipitation and is then decomposed with sulfuric acid (cf. p. 221). The free acid and its salts are used in dyeing, in medicine, and in the laboratory. Fehling's solution (p. 129) is prepared by adding sodium hydroxide and a tartrate to dilute copper sulfate solution. The deep blue solution contains a soluble complex cupric tartrate.

Isomerism of Lactic Acid and the Tartaric Acids. Tartaric acid has been shown by many reactions to be **dihydroxysuccinic acid.** It must be represented by the formula, HOOCCHOHCHOHCOOH. Yet there are three other compounds which also correspond in their reactions and transformations to the same structure. They are **laevo tartaric acid** (mp 168° to 170°); **racemic tartaric acid** (mp 205° to 206°); and **meso tartaric acid** (mp 140°). [Ordinary tartaric acid (mp 168° to 170°) is called *dextro tartaric acid.*] Similarly, lactic acid has been shown to be α-hydroxypropionic acid. But there are three lactic acids, all of which have this same structure.

A number of such exceptional cases came to light during the rapid growth of organic chemistry in the last half of the nineteenth century. They remained a mystery until van't Hoff[1] and Le Bel[2] in 1874

[1] Jacobus Henricus van't Hoff (1852–1911), Professor at the University of Amsterdam, 1877–1896, and at the University of Berlin, 1896–1911. He is famous as the joint founder of stereochemistry and for his contributions to the theory of solutions.

[2] Joseph Achille Le Bel (1847–1930), a French chemist who resided in Paris.

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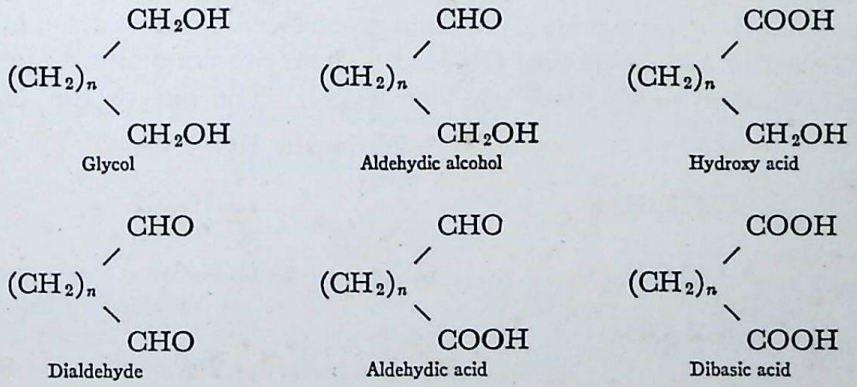
independently arrived at a solution of the problem. These scientists extended the structural theory to three dimensions, and in this way provided an explanation of these cases of isomerism which were not accounted for by the Kekulé theory. This step in the development of the structural theory is described in the next chapter.

HYDROXY ALDEHYDES AND KETONES, KETO ACIDS

Closely related to the hydroxy acids are a number of other polyfunctional compounds which contain a carbonyl group and either hydroxyl or carboxyl groups as well. These hydroxy aldehydes, hydroxy ketones, and keto acids are related systematically to the polyhydroxyl compounds as the succeeding paragraphs show. Almost all the compounds in this group which contain six carbon atoms or less are of importance to the biochemist as most of them occur in nature.

By the oxidation of a monohydric alcohol, ROH, one obtains an aldehyde or ketone and, if the alcohol was primary, eventually an acid. In the same way, the oxidation of the glycols (dihydric alcohols) will yield compounds containing the carbonyl group, and acids will be the final product if the group $-CH_2OH$ was originally present in the molecule.

The following five classes of compounds are possible oxidation products of a glycol which contains two primary hydroxyl groups (ethylene glycol, $n = 0$).



If the glycol to be oxidized contains both a primary and a secondary hydroxyl group, the following five oxidation products are possible:

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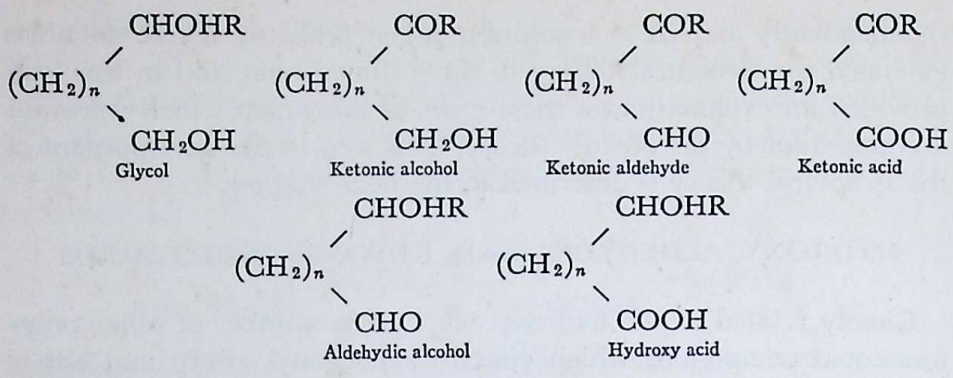
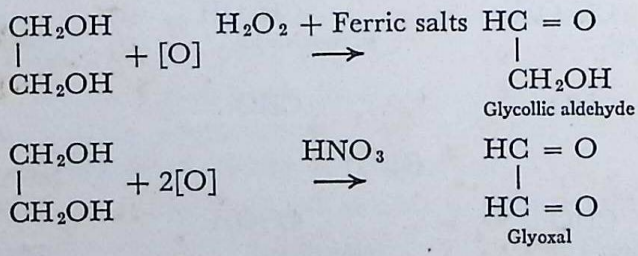


The oxidation products of a glycol which has two secondary alcohol groups would be a ketonic alcohol or a **diketone,** $RCO(CH_2)_nCOR$. A ditertiary alcohol would have no oxidation products which contained the same number of carbon atoms. Like the oxidation of a simple tertiary alcohol, the oxidation of such a compound would disrupt the molecule.

Many representatives of all the classes of compounds just outlined are known. Most of them are more conveniently prepared otherwise than by the oxidation of the glycols; but this fact does not, of course, alter their relationship to each other and to the glycols. The **dibasic acids** were considered in Chap. 11. Those compounds in which there are two carbonyl groups, or a carbonyl group and a carboxyl group separated by *one* carbon atom, have special properties. Such compounds, the **beta diketones** (or 1,3-diketones), $RCOCH_2COR$, and the **beta ketonic acids,** $RCOCH_2COOH$, form the subject matter of Chap. 14. Some representatives of the remaining types related to ethylene glycol, propylene glycol, and glycerol will be considered here.

Glycollic Aldehyde and Glyoxal. These two compounds are the first oxidation products of ethylene glycol. The one or the other



is formed depending on the nature of the oxidizing agent. When treated with alkali, glyoxal undergoes an *internal* Cannizzaro reaction (p. 149). In this interesting reaction one aldehyde group is oxidized to an acid group and the other reduced to a primary alcohol. The

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product is the sodium salt of a hydroxy acid, **glycollic acid;** the free acid is also formed by the careful oxidation of glycollic aldehyde.

$$\begin{array}{c}CHO\\|\\CHO\end{array} + NaOH \longrightarrow \begin{array}{c}CH_2OH\\|\\COONa\end{array}$$

Sodium salt of glycollic acid

$$\begin{array}{c}CH_2OH\\|\\CHO\end{array} + [O] \longrightarrow \begin{array}{c}CH_2OH\\|\\COOH\end{array}$$

Glyoxal is best prepared in the laboratory by heating acetaldehyde with **selenium dioxide.**

$$CH_3CHO + SeO_2 \longrightarrow CHOCHO + Se + H_2O$$

This oxidation reaction is applicable to all aldehydes and ketones which have the linkage $-CH_2C = O$. Thus, with butyraldehyde a similar oxidation occurs.

$$CH_3CH_2CH_2CHO + SeO_2 \longrightarrow CH_3CH_2COCHO + Se + H_2O$$

It should be noticed that hydrogen on the alpha carbon atom is attacked and not hydrogen attached to the easily oxidized carbonyl group.

Glyoxal exists in several polymeric modifications. The pure compound is a green gas with a pronounced irritating odor. In water solution it is hydrated and exists probably entirely as $CHOCH(OH)_2$. Several solid polymers are known which are formed on evaporating the solution. Both glyoxal and glycollic aldehyde react with the usual reagents which are used for characterizing aldehydes and ketones.

Glyoxylic Acid, CHOCOOH, is the aldehydic acid corresponding to ethylene glycol. It is formed by the oxidation of ethylene glycol or better, glycollic acid, or by the slow hydrolysis of chloral (p. 145) with water at an elevated temperature.

$$\begin{array}{c}CHO\\|\\CCl_3\end{array} \xrightarrow[\text{Heated}]{H_2O} \begin{array}{c}CHO\\|\\C(OH)_3\end{array} \longrightarrow \begin{array}{c}CHO\\|\\COOH\end{array}$$

Glyoxylic acid is hydrated and the anhydrous form is not known. Its formula should therefore probably be written $CH(OH)_2COOH$. In water solution it shows the typical reactions of an aldehyde. On treatment with alkali it undergoes the Cannizzaro reaction forming glycollic acid and oxalic acid.

$$2CHOCOOH + 3NaOH \longrightarrow CH_2OHCOONa + (COONa)_2 + 2H_2O$$

Acetol and Pyruvic Acid. The oxidation products of propylene glycol, $CH_3CHOHCH_2OH$, are the simplest representatives of the

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ketonic alcohols, aldehydes, and acids ($n = 0$ in the classification on p. 246). Pyruvic acid, $CH_3COCOOH$, is thus to be regarded as the final member of the following series:

$$\underset{\text{Propylene glycol}}{CH_3CHOHCH_2OH} \quad \underset{\text{Acetol}}{CH_3COCH_2OH} \quad \underset{\text{Methyl glyoxal}}{CH_3COCHO} \quad \underset{\text{Pyruvic acid}}{CH_3COCOOH.}$$

Acetol is the simplest representative of the group of the alpha hydroxy ketones or **acyloins**. Acetol itself is prepared from acetone by the following series of reactions.

$$CH_3COCH_3 \xrightarrow{Br_2} CH_3COCH_2Br \xrightarrow{CH_3COOK} CH_3COCH_2OCOCH_3 \xrightarrow{H_2O} CH_3COCH_2OH$$

Its higher homologs are prepared from esters by condensation with sodium.

$$2RCOOC_2H_5 + 4Na \longrightarrow \begin{array}{c} RCONa \\ \| \\ RCONa \end{array} + 2NaOC_2H_5$$

$$\downarrow H_2O$$

$$\begin{array}{c} RC = O \\ | \\ RCHOH \end{array}$$

The acyloins show the normal behavior of alcohols and of ketones. They also show an ease of oxidation hitherto encountered only in the aldehydes. Thus, they are oxidized by Fehling's solution.

$$CH_3COCHOHCH_3 + 2Cu(OH)_2 \longrightarrow CH_3COCOCH_3 + Cu_2O + 2H_2O$$

Acyloins react with phenylhydrazine, but the reaction does not stop with the formation of a phenylhydrazone. Instead, oxidation again takes place. The reaction with acetol may be written in the following way.

$$CH_3COCHOHCH_3 + C_6H_5NHNH_2 \longrightarrow \begin{array}{c} CH_3C = NNHC_6H_5 \\ | \\ CH_3CHOH \end{array} + H_2O$$

$$\begin{array}{c} CH_3C = NNHC_6H_5 \\ | \\ CH_3CHOH \end{array} + C_6H_5NHNH_2 \longrightarrow \begin{array}{c} CH_3C = NNHC_6H_5 \\ | \\ CH_3C = O \end{array} + C_6H_5NH_2 + NH_3$$

$$\begin{array}{c} CH_3C = NNHC_6H_5 \\ | \\ CH_3C = O \end{array} + C_6H_5NHNH_2 \longrightarrow \underset{\text{An osazone}}{\begin{array}{c} CH_3C = NNHC_6H_5 \\ | \\ CH_3C = NNHC_6H_5 \end{array}} + H_2O$$

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The final product of the reaction is the phenylhydrazone of a 1,2-dicarbonyl compound. These substances, which are known as *osazones*, are of importance in the chemistry of the sugars.

Pyruvic acid is conveniently prepared by heating racemic tartaric acid (p. 244); hence it is often called *pyroracemic acid;* the reaction involved is complicated. Pyruvic acid is of considerable importance to the biochemist, since it is an intermediate product in the changes which sugars undergo in the animal organisms (Chap. 20).

Pyruvic acid is a liquid boiling at 165° and solidifying at 14°. It has an irritating odor. It is miscible in water in all proportions. Although it contains no aldehyde group or secondary alcohol group, it is easily oxidized with the evolution of carbon dioxide. Thus it reduces an ammoniacal solution of silver nitrate.

$$CH_3COCOOH + [O] \longrightarrow CH_3COOH + CO_2$$

Glyceric Aldehyde and Dihydroxyacetone. Glycerol on mild oxidation furnishes a mixture of glyceric aldehyde and dihydroxyacetone.

$$\begin{array}{c} CH_2OH \\ | \\ CHOH \\ | \\ CH_2OH \end{array} \xrightarrow[Fe^{++}]{H_2O_2} \underset{\text{Glyceric aldehyde}}{\begin{array}{c} CHO \\ | \\ CHOH \\ | \\ CH_2OH \end{array}} + \underset{\text{Dihydroxyacetone}}{\begin{array}{c} CH_2OH \\ | \\ CO \\ | \\ CH_2OH \end{array}}$$

These products are of importance in several fields of organic chemistry and we shall encounter them a number of times. They are readily oxidized. They react with phenylhydrazine and, the reaction following the course described under acetol, both compounds furnish the same osazone.

$$\begin{array}{c} CHO \\ | \\ CHOH \\ | \\ CH_2OH \end{array} \xrightarrow{C_6H_5NHNH_2} \begin{array}{c} CH = NNHC_6H_5 \\ | \\ C = NNHC_6H_5 \\ | \\ CH_2OH \end{array} \xleftarrow{C_6H_5NHNH_2} \begin{array}{c} CH_2OH \\ | \\ C = O \\ | \\ CH_2OH \end{array}$$

QUESTIONS AND PROBLEMS

1. Outline the reactions you would use to degrade each of the following acids to simple ketones of known structure: $(CH_3)_2CHCH_2CH_2COOH$, $CH_3CH_2CH(CH_3)CH_2COOH$.

2. Write balanced equations for the reactions between phenylhydrazine and $CH_3CH_2CHOHCOCH_3$.

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3. Write structural formulas for α-hydroxybutyric acid, α,β-dibromopropionic acid, lactide, malic acid, β-hydroxypropionic acid, and ethyl tartrate.

4. Compare the behavior of $HOCH_2(CH_2)_7COOH$ and $HOOC(CH_2)_7COOH$ on heating in the presence of a catalyst. What explanation can you offer for the behavior of these two compounds as compared with $HOCH_2(CH_2)_2COOH$ and $HOOC(CH_2)_2COOH$, respectively?

5. Write equations for (*a*) the synthesis of glyoxal from ethylene, (*b*) the synthesis of $CH_3CH(COOH)_2$ from propionic acid, and (*c*) the reaction between glyoxal and sodium hydroxide.

6. What chemical test could you use to distinguish between $CH_3CHOHCH_2CH_2COCH_3$ and $CH_3CH_2CH_2CHOHCOCH_3$?

7. Why are lactones often referred to as *inner esters*? What types of compound will form lactones?

8. What products would you expect to obtain from the following reactions: (*a*) ethyl tartrate and acetic anhydride, (*b*) α-bromopropionyl bromide and absolute methyl alcohol, (*c*) sodium γ-hydroxyvalerate and hydrochloric acid, (*d*) α-hydroxyisobutyric acid and potassium permanganate.

9. Write equations for the reaction between α-chlorobutyric acid and (*a*) ammonia, (*b*) silver hydroxide, (*c*) sodium cyanide.

10. Describe and illustrate the Reformatsky reaction.

11. How would you differentiate between: (*a*) $CH_3CHClCOOH$ and $CH_3CHOHCOCl$, (*b*) $CH_3CH_2CHOHCOOH$ and $CH_3CHOHCH_2COOH$, and (*c*) $(CH_3)_2\underset{\underset{OH}{|}}{C}(CH_2)_5COOH$ and $HOCH_2(CH_2)_7COOH$?

12. Starting with glycerol, outline the synthesis of citric acid.

13. Predict the products that would be obtained from the reactions: (*a*) $CH_3COCH_2CH_2COOCH_3 + BrZnCH_2COOC_2H_5$, (*b*) diethyl tartrate + lead tetraacetate, (*c*) $CH_3CHBrCH_2COOH$ + very dilute sodium hydroxide, (*d*) butyrolactone and ethylmagnesium bromide.

14. Write balanced equations for the reactions: butyrolactone and methylaniline, malic acid and potassium permanganate, acrylic acid and hydrogen iodide, ethyl bromoacetate and potassium iodide.

15. Designate the steps in the synthesis of: (*a*) β-hydroxybutyric acid from acetaldehyde (two methods), (*b*) butyrolactone from trimethylene glycol.

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Chapter 13

OPTICAL ISOMERISM

Optical Activity. Before presenting the theory of van't Hoff and Le Bel mentioned in the preceding chapter, we must discuss briefly the phenomenon known as *optical activity*. We have seen that two of the three isomeric alpha hydroxypropionic acids are called *dextro lactic acid* and *laevo lactic acid* respectively. The words *dextro* and *laevo* refer to the fact that solutions of these substances have the property of rotating the plane of polarized light —the one to the right (dextro), the other to the left (laevo). They therefore are said to be *optically active*.

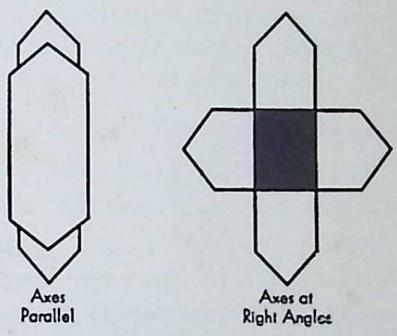

FIG. 11. Two tourmaline crystals crossed at right angles are opaque.

Polarized Light. Light which has passed through a crystal of tourmaline or a Nicol prism (a specially constructed prism of Iceland spar) is said to be *polarized*. Such light will pass through a second tourmaline crystal or Nicol prism only if it is held parallel to the first. This can be demonstrated by placing two clear tourmaline crystals one against the other and interposing them between a light and the eye. They will be transparent if their cyrstal axes are parallel; when one crystal is turned so that its axis is at right angles to that of the other, the intersection of the two crystals appears opaque (Fig. 11). If one of these crystals is now firmly set in an apparatus such as that indicated in Fig. 12 and the other placed at some distance from it on a movable axis, we have what is known as a *polariscope*. When nothing is interposed between the two crystals, the maximum amount of light can come through the apparatus and strike the eye of the observer only when the second crystal is exactly parallel to the first. If we now insert an optically active substance between the two crystals, we find that we must turn the movable crystal to the right or left in order to

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get the greatest brightness. The direction and extent of this rotation depend on the nature of the substance and the amount of it through which the light passes. A number of organic liquids and solutions of solid compounds are optically active.

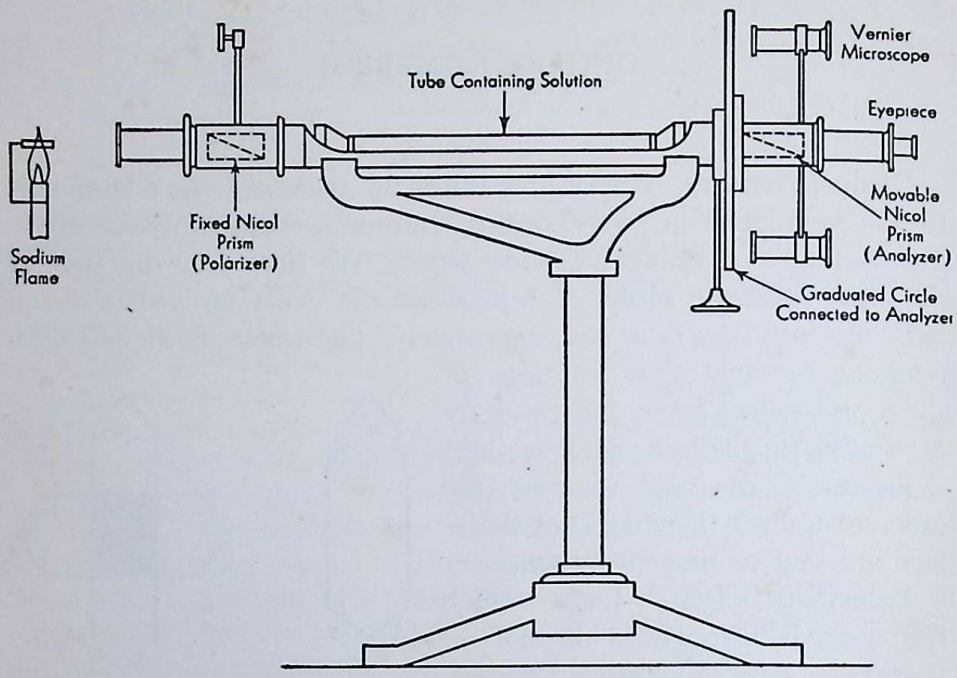

FIG. 12. Polariscope used in determining the optical activity of organic compounds. The solution of the compound is placed in the long glass tube which has parallel glass ends.

The physical explanation given for the phenomenon of optical activity is as follows: the light after passing through the first crystal is supposed to be vibrating in only one plane; therefore, the second crystal must be set in exactly the same plane in order to allow all the light to pass through it. Optically active substances have the power to rotate this plane of polarized light to the left or to the right.

The optical activity of many solids is caused by the nature of the arrangement of the molecules in the crystal; however, this phenomenon does not concern the organic chemist. *The optical activity of organic compounds is a property of the molecule* itself since it is manifested in the liquid state, in solution, and as a gas.

It is important to have a standard method of comparing the optical activity of organic liquids. The **specific rotation** of a liquid is the angular rotation (measured in a polariscope as explained above) produced by a column whose length is defined in terms of the specific gravity. Specific rotation is purposely so defined in order that

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comparable weights of material will be under observation each time. In the case of solutions, the concentration of the solution replaces the specific gravity. The two formulas for calculating the specific rotation $[\alpha]$ from an observed rotation in the polariscope ($\alpha_{obs.}$) are as follows:

$$\text{Liquids:} \quad [\alpha] = \frac{\alpha_{obs.}}{l \times \text{sp gr}}$$

$$\text{Solutions:} \quad [\alpha] = \frac{\alpha_{obs.}}{l \times c}$$

where l = length in decimeters of liquid or solution employed (usually 1 or 2 dm) and c is the weight of solute in 1 cu cm. The molecular rotation is usually defined as the specific rotation multiplied by the molecular weight and divided by a hundred. $[M] = \frac{[\alpha] \times \text{M.W.}}{100}$. Since specific rotation usually varies with the wave length of light employed in making the measurement, it is common to denote this by a small letter or number. Thus, $[\alpha]_D$ means the specific rotation measured with sodium light (D line of the spectrum), while such a symbol as $[\alpha]_{5461}$ indicates that the wave length of light employed was 5461 Ångström units (Å). The specific rotation varies somewhat with the temperature and often greatly with the nature of the solvent.

Pasteur's Separation of a Racemic Tartrate. The first important advance in the understanding of optical activity was made by Pasteur[1] in 1848. At that time racemic tartaric acid, which is optically inactive, and the common dextro tartaric acid were both known. Pasteur was studying the crystal angles of the salts of the racemic acid. He noticed on examining certain very large crystals of the sodium ammonium salt that there seemed to be two different types of crystals which differed only slightly in the position of the crystal faces. These faces were arranged either in a left-handed fashion or in a right-handed fashion with regard to the crystal axis. Thus, one type of crystal could be considered the mirror image of the other, just as one's left hand is the mirror image of the right.

Pasteur laboriously separated these left-handed and right-handed crystals into two piles, dissolved them separately in water, and examined the two solutions in the polariscope. To his delight he found that one solution turned the plane of polarized light to the right, the other an equal amount to the left, this in spite of the fact that the original salt had been entirely inactive! This classic experiment proved that in one instance, at least, the *inactive compound could be separated*

[1] Pasteur's separation of racemic tartaric acid was accomplished at the beginning of his scientific career at the age of only twenty-six. He later studied fermentation and thus became interested in microorganisms. This work led away from chemistry and toward medicine in which field he did the work with which his fame is popularly connected.

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into two active forms. It was evidently only a mixture of the well-known dextro acid and a new laevo form. The isomers were found to differ only in their effect on polarized light.

Going back from the sodium ammonium salts with which Pasteur worked to the acids from which the salts are derived, we can say that Pasteur's experiments showed that racemic tartaric acid is composed of dextro tartaric acid and laevo tartaric acid. And in fact by mixing equal quantities of laevo and dextro tartaric acids racemic tartaric acid can be obtained. These experiments therefore accounted for one of the isomeric tartaric acids. It was not possible to go further with this problem in Pasteur's time. The next step had to await the development of the structural theory, and it was not taken until some twenty-five years later by van't Hoff and Le Bel.

The Tetrahedral Carbon Atom. Le Bel and van't Hoff assumed that the valences of the carbon atoms were directed toward the corners of a more or less regular tetrahedron. To demonstrate this, they constructed solid models. These were not supposed to represent an actual picture of a carbon atom; they were only intended to show the spatial arrangement of the atoms in a molecule. The peculiar property of a tetrahedron is that *when four different things are attached to its corners, two arrangements are possible*. These differ as the *right hand differs from the left;* one arrangement is the mirror image of the other. If *two or more of the things attached to the four corners are the same, only one arrangement is possible*. This is a fact of geometry and in itself has nothing to do with chemistry; van't Hoff and Le Bel saw in it an explanation of optical activity and the isomerism which had been noted in the lactic and tartaric acids.

Optically Active Isomers Are Stereoisomers. If a tetrahedron with four different things attached can exist in two arrangements, so a carbon atom with four different atoms or groups arranged about it may exist in two forms. These two forms would be expected to differ in some right-handed or left-handed manner. This is exactly the case with optical isomers; the dextro and laevo forms are identical in all properties except their action on the plane of polarized light. According to this theory, therefore, optical isomers are stereoisomers and *differ only in the spatial arrangement of the atoms in the molecule*.

The fundamental postulate of the theory is that this isomerism is to be found only when the molecule can exist in two forms which are mirror images of each other. Such a molecule is said to be *asymmetric*. *Optical activity is a property of an asymmetric molecule*. Almost all asymmetric molecules contain an atom with four different atoms or groups

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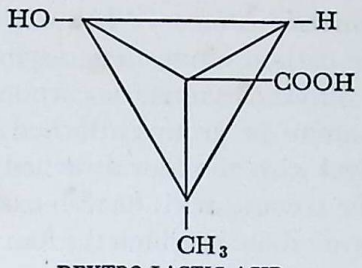
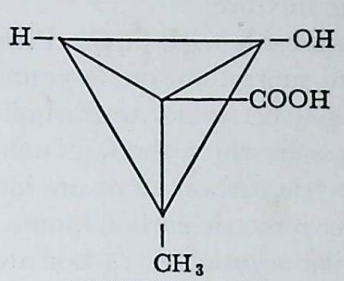
attached to it. Such an atom is called *an asymmetric atom.* However, it is possible to have an asymmetric molecule which does not contain an asymmetric atom; examples will be given later.

Compounds with One Asymmetric Carbon Atom. The Stereoisomers of Lactic Acid. The carbon atom printed **boldface** in the formula is asymmetric: $CH_3CHOHCOOH$. Models of the two forms of lactic acid are shown below.



DEXTRO LACTIC ACID



LAEVO LACTIC ACID

There is no way of telling which of the above models corresponds to the dextro acid and which to the laevo. It can only be said that if one is arbitrarily selected to correspond to the laevo form, the other must be the dextro. The racemic acid, of course, is a mixture of an equal number of molecules of the dextro and laevo forms.

If possible, the student should handle actual solid models and convince himself of the fundamental geometrical fact which is the basis of stereoisomerism. The theory predicts a dextro lactic acid, a laevo lactic acid, and a racemic mixture (inactive lactic acid). The experimental facts are in accord with this prediction. The acid which is prepared in the laboratory by synthetic methods is inactive; that formed by the fermentation of glucose may be dextro, laevo, or inactive according to the enzyme employed.

Propionic acid, CH_3CH_2COOH, contains no asymmetric carbon atom, and two different spatial arrangements are not possible. No stereoisomers are predicted, and none has ever been found. The theory of stereoisomerism has been drastically tested since it was first suggested. In every test, complete agreement has been found between the experimental facts and the predictions based on the theory.

Racemic Mixtures and Racemic Compounds. Two stereoisomers such as laevo and dextro lactic acid are sometimes spoken of as *enantiomorphs* or *enantiomers. They are identical in all physical and chemical properties except their action on polarized light.* The two isomers have the same rotating power, but turn the plane in opposite directions, one

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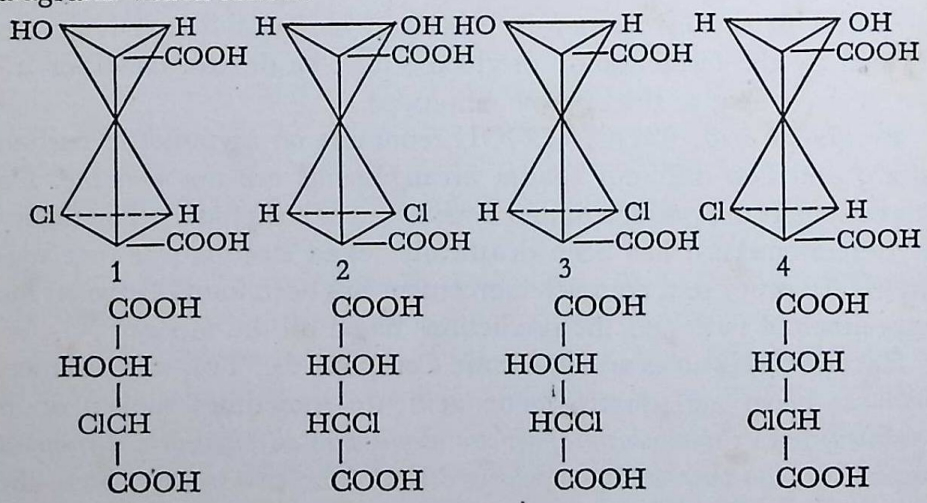
to the right and the other to the left. A mixture of two enantiomorphs may be merely a mechanical mixture of the two isomers, or it may be a loose molecular compound of the two. The first we speak of as a *racemic mixture*, the second, as a *racemic compound*. The racemic compound is met with when we are dealing with solids; it has physical properties different from those of the component isomers. In solution, it is usually largely dissociated and behaves much like a solution of a racemic mixture.

Compounds with Several Asymmetric Atoms. When a molecule contains more than one asymmetric carbon atom, these asymmetric atoms may be similar or dissimilar. Similar asymmetric carbon atoms are those in which the four unlike atoms or groups attached to one asymmetric carbon atom are identical with the four attached to the other asymmetric carbon atoms. The tartaric acids furnish examples. Dissimilar asymmetric carbon atoms are those in which the four unlike atoms or groups attached to one asymmetric carbon atom are not all identical with the four attached to the other asymmetric carbon atoms. The chlorohydroxysuccinic acids furnish examples.

```
CHOHCOOH          CHOHCOOH
|                 |
CHOHCOOH          CHClCOOH
```

Dissimilar asymmetric carbon atoms are by far the more common and the more important.

Dissimilar Asymmetric Atoms. The chlorohydroxysuccinic acids contain two dissimilar asymmetric carbon atoms. The configurations of all the stereoisomeric chlorohydroxysuccinic acids are shown in the diagrams which follow.



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It is possible in the following way to derive these four configurations and to show that they are the only configurations. Using either the models or their planar projections described in the next section, set up any one configuration and its mirror image; say numbers 1 and 2 above. Then reverse, by interchanging two substituents, the configuration of *either one* of the asymmetric carbon atoms. Set up the mirror image of this arrangement. (Reversing the configuration of the lower asymmetric carbon atom in 1 this way gives us 3.) Now complete the possibilities by reversing the configuration of the *second* asymmetric carbon atom. The configurations thus obtained will be found to be identical with two of these already derived.

We have four possible stereoisomers all of which are optically active. These four stereoisomers are the components of two racemic mixtures (or racemic compounds) as indicated above. These two different racemic mixtures differ in physical properties. The two known chlorohydroxysuccinic acids are these two racemic mixtures; they melt at 145° and 154°. Both are inactive and both are separable. Stereoisomers which are not enantiomorphs are called *diastereoisomers*, often shortened to *diamers*. Thus, 1 and 3, or 2 and 4 in the illustration above are diastereoisomers. *Not being mirror images they differ in rotation and also in their physical properties.*

By studying models it can be shown that in a compound with n dissimilar asymmetric carbon atoms there are 2^n optically active isomers and $2^n/2$ racemic mixtures.

Plane Representation of Stereochemical Formulas. Drawings of three-dimensional models such as those shown above or the models themselves are essential for the understanding of the subject of stereoisomerism. After the principles have been mastered, however, such methods of representing stereoisomers are cumbersome. A compact and convenient method of representing the models consists in projecting them onto a plane. Projections of the dibasic acids by agreement always have the carboxyl groups at the top and the bottom of the plane diagram. This corresponds to a model in which the carboxyl groups are over each other as in the drawings. Plane diagrams of the chlorohydroxysuccinic acids are shown on p. 256, just below the drawings of the three-dimensional models.

Similar Asymmetric Atoms. The tartaric acids contain two similar asymmetric atoms. Since both asymmetric atoms have the same groups about them, they will affect the plane of polarized light to the same extent, but each may be either dextro rotatory or laevo rotatory.

We are thus led to predict the following possible combinations: (1) both atoms dextrorotatory; (2) both atoms laevorotatory; (3) one atom dextro, the other laevo. In the first two, the effect of each atom

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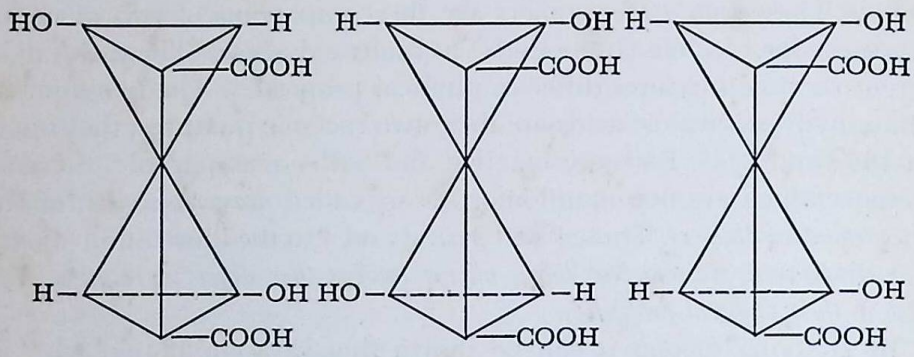
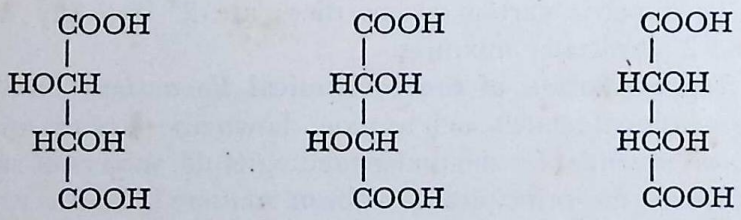
reinforces that of the other. In the third, they cancel each other, and, since the two atoms are *exactly opposite* in their effect on polarized light, the compound will be *optically inactive*. Such a compound is said to be *inactive by internal compensation*. It is not a racemic compound and obviously cannot be separated into active forms; every molecule is exactly like every other molecule and each is inactive. **Mesotartaric acid** is the isomer which is inactive by internal compensation.

The following diagrams show the spatial arrangement of the groups in dextro tartaric acid, laevo tartaric acid, and meso tartaric acid.





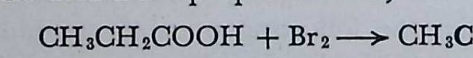
LAEVO TARTARIC ACID DEXTRO TARTARIC ACID MESO TARTARIC ACID

RACEMIC ACID

Racemic tartaric acid, as the name implies, is a racemic compound; in solution, it is a mixture of the dextro and laevo isomers. The solid is a molecular compound of one molecule each of the two forms.

The tartaric acids are remarkable in that two of the four isomers have had their original names generalized into the names of kinds of compounds. Thus the name *racemic* derives from racemic acid, and *meso* from mesotartaric acid.

Synthetic Products. We can generate an asymmetric carbon atom in two ways: by substitution, as in the preparation of α-bromopropionic acid from propionic acid;



$$CH_3CH_2COOH + Br_2 \longrightarrow CH_3CHBrCOOH + HBr$$

or by addition, as in the preparation of acetaldehyde cyanohydrin

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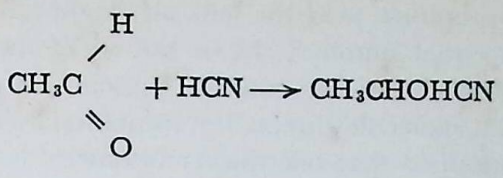
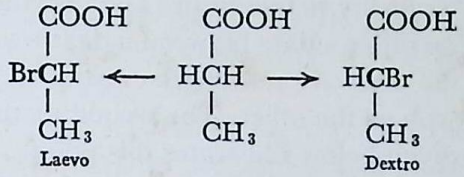
from acetaldehyde:



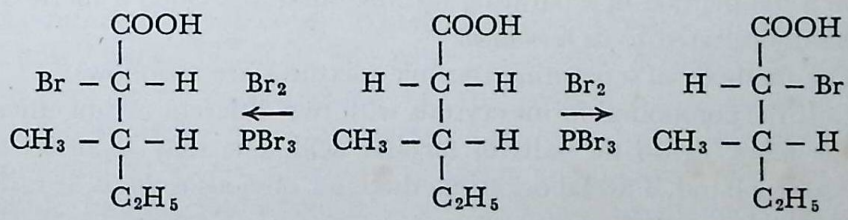
Whichever method we use, a racemic mixture (or racemic compound) results. An examination of the models shows that this result is to be expected. The two alpha hydrogen atoms in propionic acid are identical, and replacement of one of them is just as probable as is replacement of the other. If replacement of one furnishes the laevo acid, replacement of the other would furnish the dextro acid.



On the average, an equal number of dextro and laevo molecules of bromopropionic acid will be formed. The smallest amount of the product which we can examine in our polariscope contains many million molecules; even if there were one or two more dextro than laevo molecules in this sample, we could not detect their presence by our most delicate apparatus.

The student should work through for himself the reasoning that applies to the generation of an asymmetric carbon atom by addition.

When a new asymmetric carbon atom is produced by synthetic means in a molecule already optically active because of an asymmetric atom, two optically active products may be obtained. Thus, the bromination of dextro β-methylvaleric acid yields two optically active products which are not mirror images of each other.



As in the bromination of propionic acid, either the left- or right-handed hydrogen atom may be replaced; but, since the beta carbon atom is dextro and unaltered during the reaction, two substances

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+ + and + − which are different are produced. Although in the bromination of propionic acid the left- and right-handed hydrogens are replaced in equal number, this is not so in the production of diastereoisomers. For some reason the presence of an asymmetric carbon atom in a molecule directs the formation of a second asymmetric carbon atom so that one diastereoisomeric form is produced in larger amounts than the other.

Nature Produces Optically Active Compounds. The chemical transformations which take place in living things almost always produce optically active materials. This is the most striking distinction between chemical reactions in the laboratory and in plants or animals. Practically all natural products which contain an asymmetric carbon atom occur in an optically active form. The enzymes which are the natural catalysts can differentiate between a dextro and a laevo form; in their presence the odds are no longer even as to the formation of the one enantiomorph or the other. The second method of separating racemic mixtures given below illustrates this point.

Although all the physical and chemical properties of a pair of enantiomorphs are identical, their biochemical behavior is different. This is even true of drugs which manifest their chemical action by some change in a large and complex organism. In most cases where both a dextro and laevo form of a drug have been prepared, the two have been found to differ markedly in their physiological action.

Separation of Racemic Mixtures. Resolution. As we have just seen, when we synthesize compounds containing asymmetric atoms, we always obtain inactive products, racemic mixtures or compounds. As we have also seen, the two components of a racemate have identical physical properties except for their action on polarized light, and cannot be separated by crystallization or distillation. In order to be able to obtain optically active products, it is, therefore, essential to have some method of separating racemic mixtures. Such a method is generally referred to as *resolution.*

The methods of separating racemic mixtures are as follows:

1. If the compound forms crystals with two different arrangements of the faces, as do the salts of tartaric acid, one may separate the crystals by hand. This laborious method, for obvious reasons, is rarely employed.

2. If the compound is fermented by bacteria or molds, usually one of the stereoisomers will be destroyed faster than the other. In this way, by the proper choice of bacteria it is often possible to prepare

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both forms from the inactive compound. At best, however, one enantiomorph is destroyed in each separation.

3. The most general method is to combine the compound with some optically active substance. There are certain complex amines found in nature which are optically active; they are known as *alkaloids* (Chap. 32). These compounds form salts with acids. If the acid is a racemic mixture, there will be two sets of salts, corresponding to the two stereoisomers.

$$\left.\begin{array}{l}\text{Dextro acid}\\ \text{Laevo acid}\end{array}\right\} + 2 \text{ moles dextro base} \longrightarrow \begin{array}{l}\text{(I) dextro acid} - \text{dextro base}\\ \text{(II) laevo acid} - \text{dextro base}\end{array}$$

The salts I and II are not enantiomorphs. They stand in a similar relationship to each other as do the isomeric chlorohydroxysuccinic acids 1 and 3, or 2 and 4 on p. 256. That is, the salts I and II are **diastereomers;** they have different physical properties and can be separated by crystallization.

After they have been separated, the two salts can be treated *separately* with a mineral acid and the pure dextro and laevo forms of the acid can be obtained.

I. Dextro acid – dextro base + HCl ⟶ dextro acid + *d*-base hydrochloride

II. Laevo acid – dextro base + HCl ⟶ laevo acid + *d*-base hydrochloride

In a similar manner optically active acids may be used to resolve racemic mixtures which, like amines, contain a basic group.

Racemization. Some optically active compounds lose their activity on heating or treating with certain reagents. This process, which may interfere with the transformation of one optically active substance into another active compound, is known as *racemization.* Many compounds are either racemized with great difficulty or not at all. When racemization occurs readily, it is usually possible to show that some special mechanism is involved in the transformation of the + to the – isomer and vice versa.

Asymmetric Molecules Which Do Not Contain Asymmetric Carbon Atoms. It was stated earlier that optical activity and optical isomerism were consequences of an asymmetric molecule. The presence of one or more asymmetric carbon atoms is the easiest and most common way of making a molecule asymmetric. However, it is possible to secure asymmetric molecules whose asymmetry is due to other elements than carbon, and also asymmetric molecules which contain no asymmetric atoms.

Ammonium salts contain four atoms or groups covalently linked

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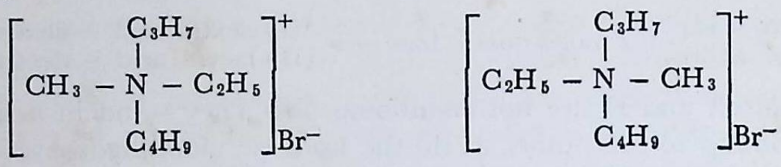
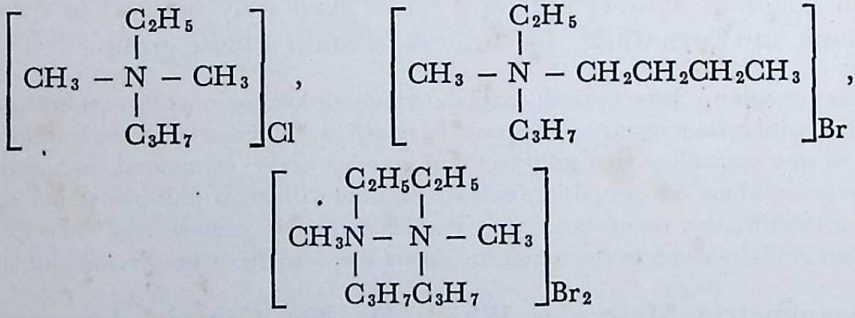
to nitrogen in the cation. If the tetrahedral arrangement is not a special property of carbon, but is to be expected whenever we have four atoms or groups covalently attached to a fifth central atom, then properly substituted ammonium salts should show optical isomerism and optical activity. This prediction has been verified by the preparation and resolution of a variety of quaternary ammonium salts. Two such isomers, containing one asymmetric nitrogen atom, are shown in projection formulas.



Asymmetry in the absence of an asymmetric atom also occurs, but in somewhat more complex molecules than we have studied up to now, so we shall not consider any examples at this time. Later, however, we shall occasionally encounter such a molecule (p. 573).

QUESTIONS AND PROBLEMS

1. Indicate the total number of stereoisomers and the number of active forms to be expected for each of the following compounds: $CH_3CHBrCHBrCOOH$, $CH_3CHClCHClCH_3$, $CH_3CHClCHBrCH_3$, $CH_3CHBrCH_3$, $CH_2OHCHOHCHOHCH_2OH$, $CH_2OH(CHOH)_4COOH$



2. Outline the steps in the resolution of $CH_3CH(C_2H_5)NH_2$.

3. Explain why the addition of bromine to propylene furnishes only inactive material.

4. Define and illustrate the following terms: *asymmetric carbon atom, racemic mixture, similar asymmetric atoms, diamers, enantiomorphs.*

5. In what ways do enantiomorphs resemble each other, and how do they differ?

6. In what ways is the following statement incorrect? "Stereoisomers are isomers which differ from each other only in their action on polarized light."

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7. Draw planar diagrams representing all the active forms of HOOCCHBrCHBrCOOH and of $CH_3CHBrCHBrCOOH$. Why does one of these compounds exist in more isomeric forms than the other?

8. In the addition of hydrogen to the inactive hydrocarbon

$$\begin{array}{l} CH_3CH-C = CHCH_3 \\ \quad\;\; | \qquad\; | \\ \quad C_2H_5 \quad CH_3 \end{array}$$

, how many isomers would you expect? Would they be active or inactive? Would they be formed in equal amounts?

9. The concentration of an optically active acid dissolved in water was 1.20 g per 100 ml of solution. A 10-ml portion had an observed rotation of 1.39° in a 10-cm polarimeter tube. Calculate the specific rotation of this substance. Why is it important to record the temperature and the solvent in reporting specific rotation?

10. Explain in detail how you would propose to separate ethyl-methyl-propyl-carbinol into its optically active components.

11. If you were to add bromine to butene-2 and to pentene-2 and were to work up the reaction mixtures by ordinary methods such as fractional crystallization or distillation, how many products would you expect to isolate?

12. Given samples of each of the four forms of tartaric acid, how would you identify each one?

13. Two forms of tartaric acid melt at 168° to 170°. When equal parts are melted together and allowed to solidify, the crystallized melt on reheating melts at 205°. Explain.

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Chapter 14

ACETOACETIC ESTER AND MALONIC ESTER

Malonic ester and acetoacetic ester are two compounds of considerable practical importance and of great theoretical interest. They are very useful in the synthesis of acids, ketones, and certain ring compounds. They form saltlike metallic compounds under certain conditions, although they contain no free carboxyl group. The constitution of acetoacetic ester was a matter of vigorous controversy for many years. We shall consider acetoacetic ester first, since a study of this substance provides the clue to the salt-forming properties of malonic ester.

Acetoacetic Ester and Acetoacetic Acid. Acetoacetic ester is prepared from ethyl acetate by the action of sodium; this reaction will be described later. It is a mobile, colorless liquid with the molecular formula $C_6H_{10}O_3$. It is obviously an ester, as on careful hydrolysis with barium hydroxide the salt of acetoacetic acid is formed. This acid on reduction yields β-hydroxybutric acid (p. 237) and from this compound acetoacetic acid is regenerated by cautious oxidation. This relationship makes it certain that acetoacetic acid has the formula, CH_3COCH_2COOH. It is a beta ketonic acid (classification, see p. 246). Its relationship to β-hydroxybutyric acid is obvious.

$$CH_3COCH_2COOH \underset{\text{Oxidation}}{\overset{\text{Reduction}}{\rightleftharpoons}} CH_3CHOHCH_2COOH$$

It very easily loses carbon dioxide on warming, forming acetone.

$$CH_3COCH_2COOH \longrightarrow CH_3COCH_3 + CO_2$$

In the urine of patients suffering from diabetes both acetoacetic acid and β-hydroxybutyric acid are usually present in considerable amounts.

The Peculiar Properties of Acetoacetic Ester. From the structure of the acid, one would conclude that the ester had the formula, $CH_3COCH_2COOC_2H_5$. Indeed, many of its reactions are exactly

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those which would be predicted from this structure. It is an ester, as has been noted; it is a ketone, as shown by its reactions with reagents which react with the carbonyl group. Peculiarly enough, it *also behaves like an hydroxyl compound.* When treated with metallic sodium it forms a metallic derivative with the evolution of hydrogen, and the same substance is formed by the action of sodium ethoxide or cold sodium hydroxide. This **sodium compound** we may represent for the present as $[CH_3COCHCOOC_2H_5]Na$, without committing ourselves as to the position of the metallic atom in the molecule. Acetoacetic ester also gives a deep color with ferric chloride. This reaction is similar to that of certain hydroxyl compounds called *phenols* which we shall meet later (p. 429). These facts and certain others led one group of chemists to contend that acetoacetic ester was in reality

$$\begin{array}{c} CH_3C{=}CHCOOC_2H_5 \\ | \\ OH \end{array}$$

and not a ketonic ester. The sodium derivative, from this point of view, would be $CH_3C(ONa) = CHCOOC_2H_5$. Others believed that the ketonic formula was correct and the sodium compound was $CH_3COCHNaCOOC_2H_5$.

The Ketonic and Enolic Forms. The discussion of the structure of acetoacetic ester and certain similar compounds finally reached a point where it seemed as if one must say that this one compound behaved as though it had two different formulas, one a ketonic formula, the other that of an unsaturated hydroxy compound. A reasonable explanation of this state of affairs would be the assumption that the liquid ester and its solutions were mixtures of two forms, the ketonic form, $CH_3COCH_2COOC_2H_5$, and the hydroxy form, $CH_3C(OH) = CHCOOC_2H_5$. This, indeed, turned out to be so. By cooling the ester to a low temperature, a crystalline solid was obtained which gave no color with ferric chloride and failed to show the other reactions which indicated an unsaturated hydroxyl compound. By acidification of the sodium compound $[CH_3COCHCOOC_2H_5]Na$ at $-78°$, an oil was obtained which showed the peculiar reactions of acetoacetic ester in a marked degree. This oil is undoubtedly the unsaturated hydroxy compound; the crystalline solid is the ketonic ester. On allowing either the solid or the liquid to stand at room temperature for some time, a liquid acetoacetic ester was formed identical in all respects to the usual compound.

The isolation of the two forms of acetoacetic ester ended the con-

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troversy. The liquid which behaved like two substances was in reality *a mixture of the* **ketonic form** *and the hydroxy compound.* The latter came to be known as the **enolic form.** The two are in a reversible equilibrium.

$$CH_3COCH_2COOC_2H_5 \rightleftharpoons CH_3\underset{\underset{OH}{|}}{C} = CHCOOC_2H_5$$

The conversion of one form into the other is rapid but not instantaneous. The enolic form has the salt-forming properties. If the equilibrium mixture (the ordinary liquid ester) is treated with sodium ethoxide, the enolic form reacts.

$$CH_3C(OH) = CHCOOC_2H_5 + C_2H_5ONa \longrightarrow$$
$$CH_3C(ONa) = CHCOOC_2H_5 + C_2H_5OH$$

As this is removed from the equilibrium, the ketonic form changes over to the enol which, in turn, is neutralized by the sodium ethoxide. Thus, eventually all the material is converted into the sodium compound.

Tautomeric Equilibria. The change of one form of acetoacetic ester into the other is spoken of as a *tautomeric change.* It will be noted that only the shift of a hydrogen atom and a double linkage is involved. The hydrogen atom in this particular system is mobile and can change places easily. The rate at which the one form shifts into the other is increased by traces of alkali. Even soft glass has sufficient alkali in it to promote the reaction. Quartz, however, does not. Therefore, if the liquid equilibrium mixture is carefully distilled in a quartz apparatus, it can be separated into the two forms. The enolic form is slightly more volatile and distills first; the pure ketonic form is left behind. On standing, each slowly changes into the same equilibrium mixture.

Methods of Determining Enolic Content. The early attempts to measure the amount of enolic or ketonic form in the liquid failed because the reagents employed reacted too slowly. The one form had sufficient time to shift into the other before the reaction was complete. For this reason, as we have seen, the equilibrium mixture behaves toward ketonic reagents as though it were all keto and toward reagents for the enolic form as though it were all enol.

The analytical method commonly used is that devised by Kurt H. Meyer. It is based on the fact that the reaction between bromine and the enolic form is extremely rapid. It consists in rapidly titrating a weighed sample with an alcoholic solution of bromine, keeping the

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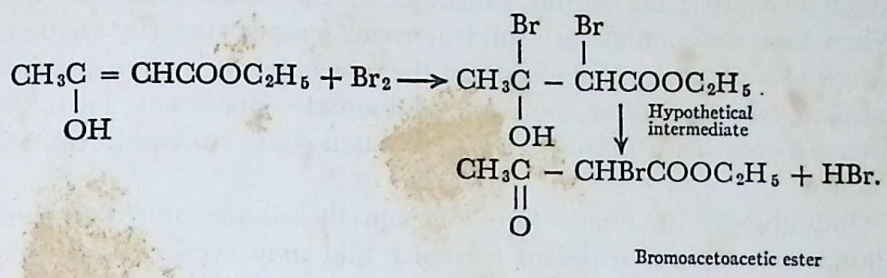
temperature at 0° to decrease the rate of rearrangement. The first slight excess of bromine is the end point which must be taken. (This excess soon disappears and eventually one molecule of bromine per mole of compound would be consumed if the titration were continued, because of the continual shift of the keto to enolic form.) The reaction is:



The ketonic form does not react with the bromine in the short time required for the titration.

It has been found by the bromine titration that the liquid equilibrium mixture of acetoacetic ester contains 93 per cent of ketonic form and only 7 of the enolic. In a solution, the composition of the equilibrium mixture depends on the nature of the solvent. For example, in water there is only 0.4 per cent enol, while in hexane there is 46 per cent.

The simple rapid titration with bromine outlined above is called the *direct method*. It can be used whenever the equilibrium is attained sufficiently slowly so that no appreciable error is introduced by shift during the titration. Where equilibrium is attained rapidly, the *indirect method*, also devised by Meyer, is used. It consists in adding as rapidly as possible (in a few seconds) an excess of an alcoholic solution of bromine. Then, *at once*, an excess of some substance which will remove all free bromine instantaneously is added. (Beta naphthol or diisobutylene, 2,4,4-trimethylpentene-2, is used for this purpose.) In this way free bromine is present for only a very short time, and the shift in equilibrium while bromine is present to react with newly formed enol is probably not serious.

All the enol has been converted into an α-bromoketone by the short exposure to bromine. The amount of α-bromoketone (and hence the amount of enol) can be determined by the reaction with hydriodic acid which has already been described on p. 145.

$$CH_3COCHBrCOOC_2H_5 + 2HI \longrightarrow CH_3COCH_2COOC_2H_5 + HBr + I_2$$

In practice an acidified solution of potassium iodide is added, and the iodine which is liberated is titrated with standard thiosulfate solution.

Enolic Forms of Other Compounds. All beta ketonic esters with the general formula $RCOCH_2COOR'$ exist in a keto and an enol

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form, but the two pure forms have been isolated in only a few cases. The beta diketones with the general formula $RCOCH_2COR'$ likewise have an enol form $\underset{\underset{OH}{|}}{RC} = CHCOR'$, and a keto form $RCOCH_2COR'$; the liquid substance is an equilibrium mixture. When such compounds are solid at room temperature (by virtue of groups of high molecular weight in the molecule), it is often possible to isolate two crystalline, isomeric compounds—one a keto form, the other an enol. In solution, or in the molten state, an equilibrium is reached.

Undoubtedly an enolic form of even the simple aldehydes and ketones can have a transient existence and may even exist in very small quantities in equilibrium with the usual ketonic form. The metallic salts of such enolic forms of the simple ketones can be prepared (in the absence of water or alcohol) by a number of methods. For example, the ketone (in ether solution) may be heated with sodamide. The following equation illustrates such a reaction with acetone.

$$CH_3COCH_3 + NaNH_2 \longrightarrow CH_3\underset{\underset{ONa}{|}}{C} = CH_2 + NH_3$$

These metallic derivatives of the simple ketones are decomposed by water, acid, or even alcohol, regenerating the ketone. All attempts have so far failed to obtain evidence of the existence of the enol form which is presumably the first product; it must shift into the ketonic form very rapidly.

$$CH_3\underset{\underset{ONa}{|}}{C} = CH_2 + C_2H_5OH \longrightarrow CH_3\underset{\underset{OH}{|}}{C} = CH_2 + C_2H_5ONa$$

$$\downarrow \text{Very rapidly}$$

$$CH_3COCH_3$$

The table (p. 269) gives the percentage of enol in equilibrium with the ketonic form at room temperature for a number of substances. (All compounds are compared in dilute alcoholic solution.)It is evident that the beta diketones and beta ketonic esters occupy an intermediate position between the beta ketonic aldehydes, which are practically entirely enolic, and the simple ketones, which are almost entirely ketonic. In general, it is found that enolization is increased by the presence of the following unsaturated groups (often called

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SUMMARY OF ENOLIZATION OF SIMPLE CARBONYL COMPOUNDS

Name	*Enolic Form*	*Ketonic Form*	*Per Cent Enol at Equilibrium in Dilute Solution*
Beta ketonic aldehydes	$RCOCH = CHOH$	$RCOCH_2CHO$	Greater than 98 per cent
Acetylacetone (1,3 diketone)	$CH_3COCH = CCH_3$ (OH)	$CH_3COCH_2COCH_3$	83 per cent
Methylacetylacetone	$CH_3COC(CH_3) = CCH_3$ (OH)	$CH_3COCH(CH_3)COCH_3$	31 per cent
Acetoacetic ester	$CH_3C(OH) = CHCOOC_2H_5$	$CH_3COCH_2COOC_2H_5$	10 per cent
Methylacetoacetic ester	$CH_3C(OH) = CCOOC_2H_5$ (CH_3)	$CH_3COCH(CH_3)COOC_2H_5$	4 per cent
Malonic ester	$C_2H_5OC(OH) = CHCOOC_2H_5$	$C_2H_5OCOCH_2COOC_2H_5$	Less than 0.01 per cent
Simple ketones and aldehydes	$RC(OH) = CHR$	$RCOCH_2R$	Much less than 0.01 per cent

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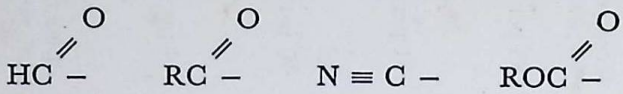
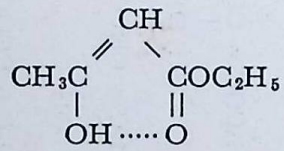
negative groups) attached to the alpha carbon atom (i.e., in the beta position to the carbonyl group).



These same groups in any other position in the molecule are without effect. For example, $CH_3COCH_2CH_2COOC_2H_5$ shows none of the peculiar properties of acetoacetic ester, but is like acetone.

Hydrogen Bonding and Resonance in the Enol of Acetoacetic Ester. The enolic form of acetoacetic ester has a lower boiling point than the ketonic form. By analogy with simple compounds one would predict that the enol would be higher boiling, since alcohols boil higher than the corresponding ketones; e.g., isopropyl alcohol boils at 82°, acetone at 56°. An explanation for the lower boiling point and for certain other unusual physical properties of the enol is to be found in hydrogen bonding and resonance. In enolic acetoacetic ester and in other enols containing the grouping $\underset{\underset{OH}{|}}{C} = CH - \underset{\underset{O}{\|}}{C}$, it is possible for an intramolecular hydrogen bond to form (cf., p. 83).



This takes place instead of the intermolecular hydrogen bonding that occurs with simple alcohols and which leads to association and the high boiling points characteristic of the simple alcohols.

The existence and stability of enols in compounds containing the system $\underset{\underset{OH}{|}}{C} = CH - \underset{\underset{O}{\|}}{C}$, as opposed to simple carbonyl compounds such as acetone and compounds such as laevulinic ester, $CH_3COCH_2CH_2COOC_2H_5$, is probably due to the stabilization of the enol by resonance energy. Resonance comparable to that in the undissociated aliphatic acids (p. 80) can occur in the undissociated enol. In the undissociated enol, however, the hydroxyl and carbonyl groups are not attached as they are in the acids, but are separated by

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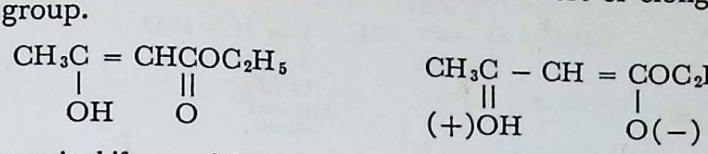
a vinyl group, CH = CH. The enol is thus a sort of elongated carboxyl group.



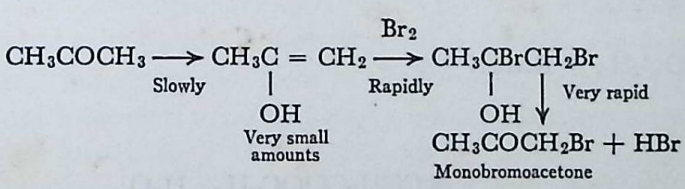
Tautomeric shifts are of the type where the same number of molecules occur on both sides of the reaction; therefore, the heat of the reaction and the equilibrium constant go hand in hand. In those compounds where the enol is stabilized by hydrogen bonding and resonance, the value of $K = \frac{(\text{Enol})}{(\text{Keto})}$ runs from 10^2 (beta ketonic aldehydes) to about 10^{-1} (acetoacetic ester). The heat evolution in the reaction is correspondingly small. For simple aldehydes and ketones, the value of K is probably of the order of 10^{-4} to 10^{-8}, and the reaction,

$$\text{enol} \longrightarrow \text{keto},$$

is exothermic by 5 to 10 kg-cal, though no accurate measurements are available since the pure enolic forms cannot be isolated.

Some metallic derivatives of the enols have the metal held by covalences to the oxygen atoms. These derivatives, for example, the copper and beryllium compounds, are nonpolar, volatile, and soluble in organic solvents. Metallic derivatives of this sort have been given the name of *chelate compounds*. Other metallic derivatives, the sodium derivatives for instance, are saltlike, polar substances.

Enolization as an Explanation of Certain Reactions. Attention has been repeatedly called to the unusual reactivity of the alpha hydrogen in aldehydes, ketones, acid chlorides, and esters. For example, it is this hydrogen atom which is so relatively easily replaced by halogen (pp. 100 and 145) and which is involved in certain condensation reactions (p. 137). It seems very probable that this reactivity is due to the fact that the hydrogen in the alpha position can enolize, and that the enolic form is involved in the reactions. For example, the bromination of acetone probably proceeds through the following steps:



Similar reactions may be written for other halogenations involving a hydrogen on a carbon atom alpha to a carbonyl group.

In the aldol condensation and many similar processes, a small amount of enol may be the actual reactant. For example, the following mechanism has been suggested for the formation of aldol (p. 137).

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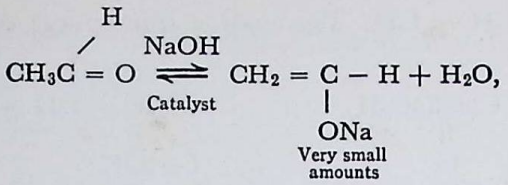

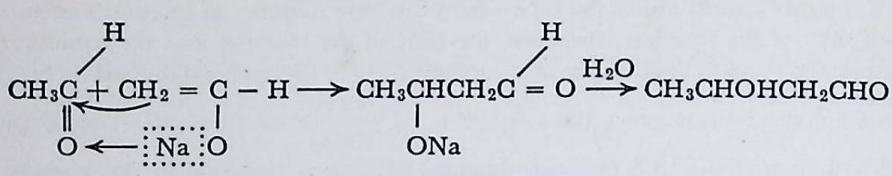

Ester Condensations. The preparation of acetoacetic ester illustrates a general reaction of esters which contain the $-CH_2COOR$ grouping. The condensing agents most frequently used in the reaction are metallic sodium and sodium ethoxide. The condensation is an equilibrium process.

$$2RCH_2COOC_2H_5 + NaOC_2H_5 \rightleftharpoons \underset{\substack{|\\ ONa}}{RCH_2C} = C(R)COOC_2H_5 + 2C_2H_5OH$$

If the equilibrium is shifted to the right by removing the alcohol formed in the condensation, yields of acetoacetic ester as high as 80 per cent of the theoretical amount can be obtained. As the group R in the ester becomes larger, both the rate of attaining equilibrium and the extent of condensation decrease.

The condensation of esters of two different fatty acids is not a useful reaction. Special methods are therefore necessary to make such beta ketonic esters as $CH_3CH_2COCH_2COOC_2H_5$. We shall indicate one method.

$$\underset{\substack{|||\\ N}}{C}CH_2COOC_2H_5 + RMgX \longrightarrow \underset{\substack{||\\ NMgX}}{RC}CH_2COOC_2H_5 \xrightarrow[HX]{H_2O} \underset{\substack{||\\ O}}{RC}CH_2COOC_2H_5$$

The condensation of an ester such as ethyl acetate with the ester of

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a dibasic acid, for example, ethyl oxalate, can be used for preparative purposes.

$$\begin{array}{l} COOC_2H_5 \\ | \\ COOC_2H_5 \end{array} + CH_3COOC_2H_5 \xrightleftharpoons{NaOC_2H_5} \underset{\text{Ethyl oxalacetate}}{\begin{array}{l} COCH_2COOC_2H_5 \\ | \\ COOC_2H_5 \end{array}}$$

Esters will also condense with ketones to form beta diketones.

$$CH_3CO\boxed{OC_2H_5 + H}CH_2COCH_3 \xrightleftharpoons{Na} \underset{\text{Acetylacetone}}{CH_3COCH_2COCH_3} + C_2H_5OH$$

It should be noticed that these ester condensations are connected with the enhanced reactivity of the α-hydrogen atoms (p. 271). It is probable that the first step is the formation of a sodium compound of the enolate of the ester; this adds to the carbonyl group of a second molecule of ester. The resulting complex

$$\begin{array}{l} \quad\quad\quad\quad ONa \\ \quad\quad\quad\quad / \\ R'CH_2C - OCH_3 \\ \quad\quad\quad\quad \backslash \\ \quad\quad\quad\quad CHCOOCH_3 \\ \quad\quad\quad\quad | \\ \quad\quad\quad\quad R' \end{array}$$

loses the elements of sodium methoxide to give the corresponding ketonic ester.

Malonic Ester. Ethyl malonate or malonic ester, $CH_2(COOC_2H_5)_2$, occupies a position intermediate between acetoacetic ester and a simple ketone like acetone. The equilibrium mixture contains too little enolic form to be detected; indeed the enolic form has never been isolated. However, clear evidence for the existence of such a form may be obtained. If the sodium compound, $C_2H_5OOCCH = C(ONa)OC_2H_5$, is acidified at a low temperature, an oil is produced which contains a large amount of the enolic form as determined by Meyer's method. This oil rapidly reverts to the ordinary malonic ester in which no enolic form can be found.

Malonic ester differs from acetone in that the sodium derivative of the enolic form is stable in alcohol solutions. This fact has enormous practical consequences, since it enables us to prepare **sodium malonic ester** by the action of sodium ethoxide on the ester itself. As we shall see in the next paragraphs, this sodium derivative, like that of aceto-

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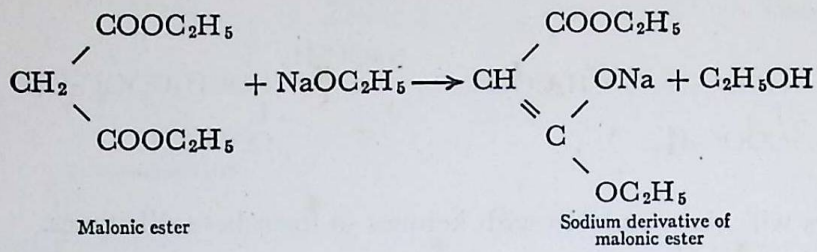
acetic ester, is of great value in synthesis:



The ethyl ester of malonic acid is almost always the ester employed in the laboratory though the methyl ester will serve equally well. **Ethyl malonate** (malonic ester) is a liquid boiling at 198°. It is formed by esterifying malonic acid in the usual way, or directly from the half nitrile of malonic acid (cyanoacetic acid) by the direct action of alcohol and acid (p. 224). On hydrolysis ethyl malonate yields malonic acid. It should be noted that there is no evidence of the formation of any enolic form of *malonic acid* itself. It is also important to distinguish clearly between the sodium derivative of malonic ester (also called the *sodium salt* of malonic ester) and the usual salts of malonic *acid*, such as $CH_2(COONa)_2$, sodium malonate. *Malonic ester resembles acetoacetic ester in that it readily forms a sodium salt, but differs from acetoacetic ester in that the pure liquid contains no appreciable quantity of an enolic form.*

USE OF MALONIC ESTER IN SYNTHESIS

Alkylation of Malonic Ester. The sodium compound of malonic ester reacts rapidly with alkyl halides, forming compounds in which the alkyl group is attached to the central carbon atom.

$$Na[CH(COOC_2H_5)_2] + CH_3I \longrightarrow CH_3CH(COOC_2H_5)_2 + NaI$$

The fact that the methyl group is found linked to *carbon instead of oxygen* constitutes an exception to the general rule in organic reactions that in a replacement reaction the entering atom or group takes the place of the atom which is removed. There can be no doubt of the facts, however, as the product on hydrolysis yields a dibasic acid, $CH_3CH(COOH)_2$. This on heating loses carbon dioxide and forms propionic acid.

$$CH_3CH(COOH)_2 \xrightarrow[140°]{} CH_3CH_2COOH + CO_2$$

It will be recalled that malonic acid loses carbon dioxide when heated, and the alkyl derivatives have the same property.

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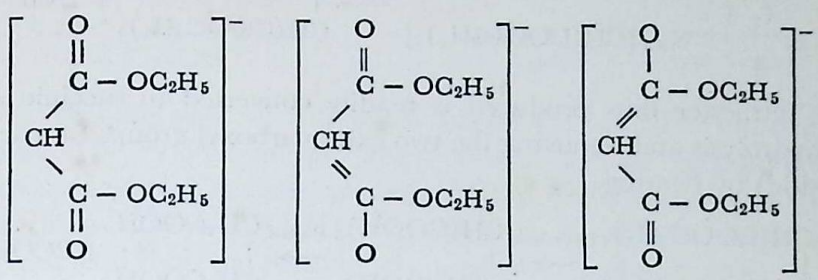
We used a noncommittal formula for the sodium compound of malonic ester in writing the alkylation reaction with methyl iodide. This is the usual practice, but it must be kept in mind that the anion of the metallic derivative is a resonance hybrid and that one of the contributing forms (the first one written below) would give rise to the alkylation product actually obtained.



The combination of the two reactions just mentioned, alkylation and loss of carbon dioxide, is very valuable in the synthesis of acids. In the example above, propionic acid was synthesized. If ethyl iodide is used in place of the methyl compound, the final product is butyric acid. Any simple alkyl halide can be used in this reaction. Secondary halides react with difficulty, and tertiary halides cannot be employed.

Synthesis of Forked-Chain Acids. In addition to its use in preparing straight-chain acids, malonic ester can be used in preparing acids with a branch in the chain next to the carboxyl group. This is possible because the monoalkyl malonic esters, $RCH(COOC_2H_5)_2$, also form sodium salts, which in turn will react with alkyl halides. Using RX and R′X to indicate two alkyl halides (with the same or different alkyl groups), we may outline the steps in this synthesis as follows:

$$CH_2(COOC_2H_5)_2 \xrightarrow{C_2H_5ONa} Na[CH(COOC_2H_5)_2] \xrightarrow{RX}$$

$$RCH(COOC_2H_5)_2 \xrightarrow{C_2H_5ONa} Na[RC(COOC_2H_5)_2] \xrightarrow{R'X}$$

$$RR'C(COOC_2H_5)_2 \xrightarrow{NaOH} RR'(COONa)_2 \xrightarrow{Acid}$$

$$RR'(COOH)_2 \xrightarrow{Heat} \begin{matrix} R \\ R' \end{matrix}\!\!>CHCOOH$$

Synthesis of Dibasic Acids. Malonic ester may be used very advantageously in the synthesis of dibasic acids. The simplest illustration is the preparation of succinic acid. The essential reaction here is between iodine and sodium malonic ester. The iodine combines with

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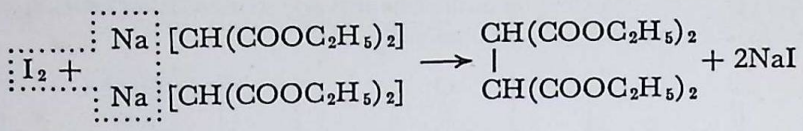
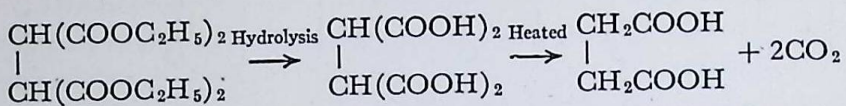
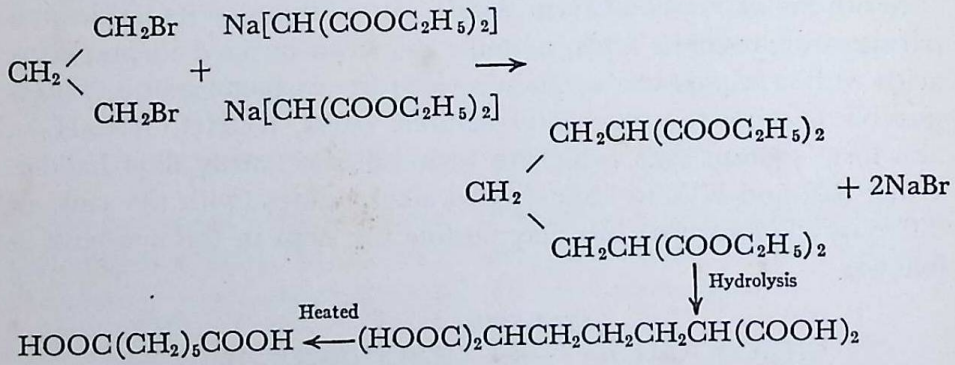
the sodium, and two malonic ester residues join together at the central carbon atoms.



The tetraester thus produced is readily converted to succinic acid by hydrolysis and removing the two extra carboxyl groups (as carbon dioxide) by heating.



A different reaction is involved in the synthesis of acids of the type $HOOC(CH_2)_nCOOH$. Here we may start with a dihalide, $CH_2Br(CH_2)_xCH_2Br$, having four less carbon atoms than the desired acid. Both ends of the chain react in a normal way as the reaction with trimethylene bromide illustrates.



USES OF ACETOACETIC ESTER IN SYNTHESIS

The use of acetoacetic ester in synthetical work depends largely on two types of decomposition which acetoacetic ester and its alkyl derivatives undergo when treated with alkali. If a *dilute* alkaline solution is employed, the ester group is first hydrolyzed and the resulting sodium salt of acetoacetic acid (or substituted acetoacetic acid) loses carbon dioxide when the solution is acidified. Inorganic acids may be used in place of dilute alkali and with the same result. If *concentrated* sodium hydroxide is employed, however, the molecule cleaves in such a way as to produce the sodium salts of two acids.

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These two methods of decomposition are illustrated by the following diagrams:

"Ketonic cleavage" with *dilute* NaOH or acids

$$\begin{array}{r|ll|l} CH_3COCH_2 & COO & & C_2H_5 \\ H & OH & H & OH \end{array}$$

"Acid cleavage" with *concentrated* NaOH

$$\begin{array}{r|ll|l} CH_3CO & CH_2COO & & C_2H_5. \\ NaO & H & Na & OH \end{array}$$

The "ketonic cleavage" is taken advantage of in the synthesis of ketones. The "acid cleavage" may be used for the preparation of substituted acids. Thus, the cleavage of $CH_3COCR_2COOC_2H_5$ would yield the acid $R_2CHCOOH$. This method of synthesizing acids is now less used than the method which employs malonic ester.

Acetoacetic Ester Synthesis of Ketones. The alkylation of the sodium salt of acetoacetic ester parallels the alkylation of malonic ester.

$$Na[CH_3COCHCOOC_2H_5] + CH_3I \longrightarrow CH_3COCH(CH_3)COOC_2H_5 + NaI$$

The process can be repeated, also, and compounds of the type $CH_3COC(R)(R')COOC_2H_5$ are formed. When these are treated with dilute alkali, the "ketonic cleavage" takes place, the ketone CH_3COCHR_2 being formed. From a monosubstituted acetoacetic ester, $CH_3COCHRCOOC_2H_5$, a methyl ketone, CH_3COCH_2R, is formed. The steps in the synthesis of methyl isopropyl ketone will illustrate the procedure.

$$\begin{array}{ccc}
CH_3COCH_2COOC_2H_5 & \xrightarrow{NaOC_2H_5} & Na[CH_3COCHCOOC_2H_5] \\
 & & \downarrow CH_3I \\
Na[CH_3COCCH_3COOC_2H_5] & \xleftarrow{NaOC_2H_5} & CH_3COCH(CH_3)COOC_2H_5 \\
\downarrow CH_3I & & \\
CH_3COC(CH_3)_2COOC_2H_5 & & \\
\downarrow \text{Saponification followed by acidification} & & \\
CH_3COCH(CH_3)_2 & &
\end{array}$$

Certain Other Uses of Acetoacetic Ester. A great variety of compounds containing the grouping $CH_3COCH\langle$ may be prepared from acetoacetic ester. The synthesis of laevulinic acid,

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$CH_3COCH_2CH_2COOH$, will serve as one illustration:

$$Na[CH_3COCHCOOC_2H_5] + ClCH_2COOC_2H_5 \longrightarrow$$

$$\underset{\underset{CH_2COOC_2H_5}{|}}{CH_3COCHCOOC_2H_5} \xrightarrow[\text{Ketonic cleavage}]{\text{Dil. NaOH}} CH_3COCH_2CH_2COOH$$

Direct Aikylation of Ketones. Acetone and other simple ketones will react with sodamide ($NaNH_2$) in dry ether to form metallic derivatives. These compounds can be alkylated, and, just as in the alkylation of acetoacetic ester or malonic ester, the *alkyl group becomes attached to carbon.* The direct alkylation of acetone by this procedure with methyl iodide yields first methyl ethyl ketone, $CH_3COCH_2CH_3$.

$$CH_3COCH_3 + NaNH_2 \longrightarrow [CH_3COCH_2]Na + NH_3$$

$$[CH_3COCH_2]Na + CH_3I \longrightarrow CH_3COCH_2CH_3 + NaI$$

On treatment again with sodamide and then a further amount of methyl iodide, a mixture of two ketones is produced: $CH_3CH_2COCH_2CH_3$ and $CH_3COCH(CH_3)_2$. The process may be repeated until **hexamethylacetone,** $(CH_3)_3CCOC(CH_3)_3$, is formed. This interesting substance has already been referred to as showing almost none of the typical reactions of a ketone (p. 161).

QUESTIONS AND PROBLEMS

1. What would you expect to have happen if acetoacetic ester were distilled in a quartz apparatus, but some pieces of soft glass were added to the ester in the distilling flask?

2. What is the explanation for the fact that the enol of acetoacetic ester is lower boiling than the ketonic form?

3. If 0.1720 g of $CH_3CH_2COCH_2COOC_2H_5$ in a Kurt Meyer titration was found to liberate 0.03045 g of iodine, what was the percentage of enol in the sample?

4. Outline the steps in the synthesis of the following acids from malonic ester: $(CH_3)_2CHCH_2COOH$, $\underset{\underset{C_2H_5}{|}}{CH_3CHCOOH}$, $(CH_3)_2C(COOH)_2$, $CH_3CH_2CH_2CH_2COOH$.

5. Write structural formulas for the resonating forms of the sodium derivative of malonic ester.

6. What experimental conditions would you use for:

a. the direct alkylation of acetone with ethyl bromide
b. the ketonic cleavage of $CH_3COCH(CH_2CH_2CH_2CH_3)COOC_2H_5$
c. the alkylation of $CH_3COCH_2COCH_3$ with methyl iodide
d. the acid cleavage of $CH_3COC(CH_3)_2COOC_2H_5$.

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7. Outline the steps in the preparation of $CH_3COCH_2CH_2CH_2CH_2CH_3$, $CH_3COCH(CH_3)(C_2H_5)$, and $CH_3COCH(C_2H_5)_2$ from acetoacetic ester.

8. Compare and contrast the isomerism shown by the following pairs of compounds: ethyl alcohol and methyl ether, *n*-propyl and isopropyl alcohols, dextro lactic acid and laevo lactic acid, keto and enol acetoacetic ester, meso and racemic tartaric acids.

9. Outline the evidence that liquid acetoacetic ester is an equilibrium mixture of a ketonic and an enolic form.

10. How could you distinguish by chemical tests between:

a. $CH_3CH_2COCH_2COOC_2H_5$ and $CH_3COCH_2CH_2COOC_2H_5$
b. $CH_3COCHBrCOOC_2H_5$ and $CH_2BrCH_2COCH_2COOCH_3$
c. $CH_2(COOC_2H_5)_2$ and $(CH_3)_2C(COOCH_3)_2$.

11. Predict the results of the action of sodium ethoxide on:

a. a mixture of ethyl oxalate and ethyl acetate
b. $CH_3CH_2CH(COOC_2H_5)_2$
c. $CH_3CH_2COCH_2CN$
d. a mixture of ethyl acetate and acetone
e. CH_3COCH_2CHO
f. $CH_3COCH_2CH_3$
g. CH_3CH_2CHO.

12. Would you expect to be able to resolve $CH_3CO\overset{\overset{CH_3}{|}}{C}HCOOC_2H_5$ into active forms? Why?

13. Describe with equations the method for preparing:

$CH_3COCH_2COOC_2H_5$, $CH_3CH_2COCH_2COCH_3$, $CH_3CH_2CO\underset{\underset{CH_3}{|}}{C}HCOOC_2H_5$.

14. Which of the following compounds would you expect to form a metallic derivative when treated with C_2H_5ONa in absolute ether? CH_3COCH_2CN, $CH_2(CHO)_2$, $CH_3COCOOH$, $CH_3COC(CH_3)_2COCH_3$, $CH_3COCH(CH_3)COC_2H_5$.

15. Compare the tautomerism of the following: CH_3COCH_2CHO, $CH_3COCH_2COOC_2H_5$ and $CH_2(COOC_2H_5)_2$. What experimental evidence indicates that malonic ester can exist in the enol form?

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Chapter 15

THE CARBOHYDRATES

Sugar, starch, and cellulose are common examples of a class of substances known as the *carbohydrates*. This name originated from the fact that the empirical formula of these compounds and many other carbohydrates can also be written as $C_y(H_2O)_x$; e.g., glucose, $C_6H_{12}O_6$, $(C_6(H_2O)_6)$, and cane sugar, $C_{12}H_{22}O_{11}$, $(C_{12}(H_2O)_{11})$. Such formulas have no structural significance, of course.

The carbohydrates are divided into three classes: the **monosaccharides,** the **disaccharides,** and the **polysaccharides.** The monosaccharides are **polyhydroxy aldehydes** or **polyhydroxy ketones.** The disaccharides and polysaccharides, on hydrolysis, yield monosaccharides. A knowledge of the monosaccharides, therefore, is essential to an understanding of the more complex carbohydrates.

MONOSACCHARIDES

Glucose, $C_6H_{12}O_6$, also known as *dextrose* or *grape sugar*, is the commonest monosaccharide and occurs widely distributed in nature. Its commercial manufacture from starch will be discussed later (p. 301). The structure and the reactions of glucose are complex and are best presented in the stepwise, historical order in which they were worked out by several generations of organic chemists.

The following facts are of importance in determining the constitution of glucose: (1) glucose is easily oxidized to an acid of the formula $C_6H_{12}O_7$; (2) it forms a pentaacetate, $C_6H_7O(OCOCH_3)_5$, when treated with acetic anhydride; (3) on reduction with hydrogen iodide and phosphorus (above 100°), a mixture of *n*-hexyl iodide and secondary hexyl iodide is formed. From this third fact we can conclude that the six carbon atoms in glucose are arranged in a straight chain, and from the second, that there are five hydroxyl groups in the molecule. The oxidation reaction indicates that the substance is an aldehyde. In connection with this last conclusion it will be recalled that an aldehyde RCHO is easily oxidized to an acid RCOOH; primary alcohols are also oxidized to acids, but there is a loss of two

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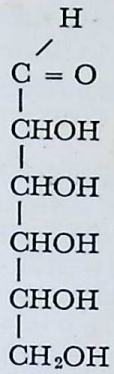
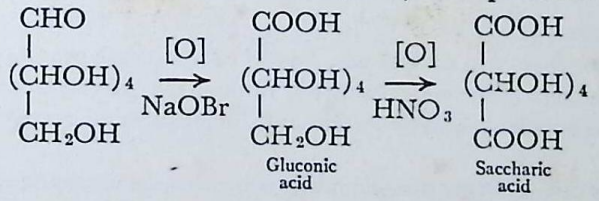
hydrogen atoms. The acid from glucose has the same number of both carbon and hydrogen atoms as the sugar itself and, therefore, an aldehyde group and not an alcohol group is involved in the oxidation. One of the five hydroxyl groups is that of a primary alcohol since a *dibasic* acid with six carbon atoms and four hydroxyl groups can be prepared by drastic oxidation.

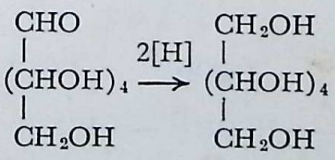
Since it has been found that the occurrence of two or more hydroxyl groups on the *same* carbon atom is very unusual, we may distribute the 5 hydroxyl groups on five of the six carbon atoms of the straight chain. This leaves the terminal carbon atom for the aldehydic group.



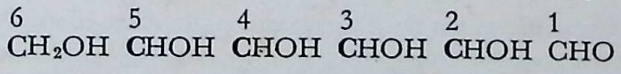
This formula accounts satisfactorily for most of the reactions of glucose. Thus, the oxidation of glucose to a monobasic acid, *gluconic acid*, and to a dibasic acid, *saccharic acid*, may be represented as follows.



Similarly, the reduction of glucose to the hexahydroxy compound, *sorbitol* or *sorbite*, may be represented:



The Aldohexoses. The formula for glucose shows the existence of four asymmetric carbon atoms (indicated by **heavy type**).



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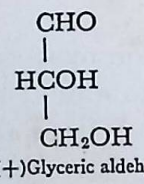
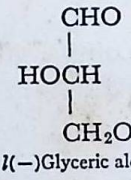
The number of possible stereoisomers of a substance with this formula is 2^4 or 16. Glucose is only one of these sixteen isomers; it is scientifically known as *d-glucose*, its enantiomorph as *l-glucose*. All the isomers are known; some occur in nature and others have been prepared in the laboratory. This group of sixteen stereoisomers is known as the *group of aldohexoses*.

Sugars which have an aldehydic group are called *aldoses;* those which contain a ketonic group *ketoses*. The number of carbon atoms in the sugar can also be indicated in the name. Thus, the **hexoses** are all sugars with six carbon atoms; the **pentoses** with five. The name *aldohexose* indicates a six-carbon sugar with an aldehydic group. Similarly the name *aldopentose* indicates a five-carbon sugar with an aldehydic group and the name *ketohexose* a ketonic sugar with six carbon atoms.

The methods of determining the spatial relationship of the asymmetric atoms in the isomeric sugars are too complicated and specialized for inclusion in a first course in organic chemistry. We shall only indicate here the methods used and the results obtained. Glyceric aldehyde (p. 249) is taken as a reference compound and *by agreement* the two active forms of the aldehyde are represented by the following spatial formulas.



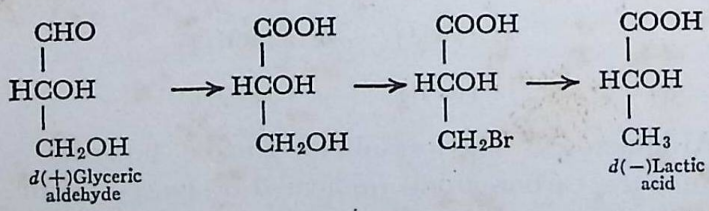
d(+)Glyceric aldehyde



l(−)Glyceric aldehyde

In the names for these two compounds, *d* and *l* refer to configuration while (+) and (−) refer to the sign of the optical activity. In these two reference compounds *d* configuration accompanies positive rotation and *l* configuration accompanies negative rotation.

Then one of the reference compounds is converted, *by reactions which do not involve substitution on the asymmetric carbon atom*, into the substance whose configuration is to be established. Thus we may indicate the conversion of *d*(+)glyceric aldehyde into an optically active lactic acid.



d(+)Glyceric aldehyde

d(−)Lactic acid

The lactic acid so obtained has the *d* configuration, the same configuration as *d*-glyceric aldehyde; but it is laevorotatory, so we designate it *d*(−)lactic acid.

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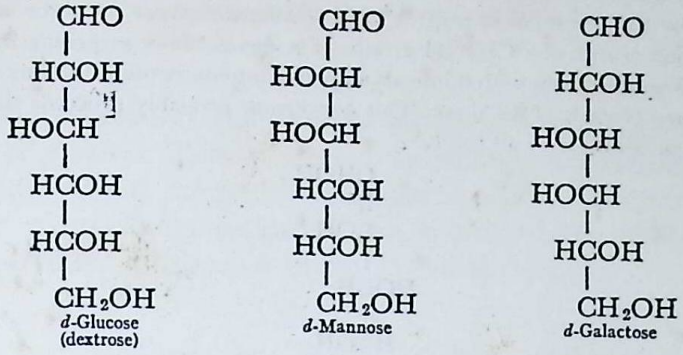
This same sort of process repeated many times enables configurations to be worked out for the monosaccharides. By agreement, the configuration of the fifth carbon atom, the carbon atom next to the CH_2OH group, is the basis for assigning the *d* or *l* configuration. The configurations of the three naturally occurring aldohexoses are the following:

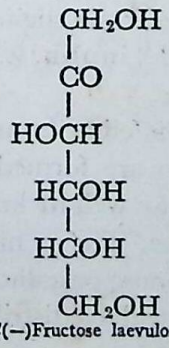


Other Aldohexoses of Importance. Besides the very important sugar, *d*-glucose (dextrose), two other of the sixteen possible isomers should be particularly mentioned. These are ***d*-mannose** and ***d*-galactose** whose configurations have just been represented. It will be noted that mannose differs from glucose only by having the opposite spatial arrangement of the hydroxyl group nearest the carbonyl. It is, therefore, said to be the *epimer* of glucose. It may be prepared by the hydrolysis of ivory-nut fragments. ***d*-Galactose** is contained in the cell walls of plants in polymerized anhydro forms known as *galactans*. It is formed by the hydrolysis of such substances and of other vegetable materials known as *pectins*. Together with *d*-glucose, it is formed by the hydrolysis of milk sugar (lactose).

Laevulose, a Ketohexose. The ketohexoses are a class of sugars represented by the following general formula (asymmetric atoms printed in heavy type).

$$\overset{6}{CH_2OH}\ \overset{5}{\mathbf{C}HOH}\ \overset{4}{\mathbf{C}HOH}\ \overset{3}{\mathbf{C}HOH}\ \overset{2}{CO}\ \overset{1}{CH_2OH}$$

There are 2^3 or 8 isomeric ketohexoses. Of these only one is of general interest. This is ***d*(−)fructose**, commonly called *laevulose* or *fruit sugar*. The configurational formula is as follows:



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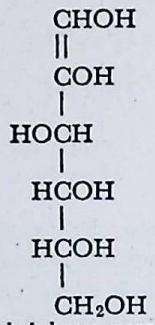
The name assigned this sugar illustrates the use of the italicized *d* or *l* to indicate configuration, and the parenthesized + or − to indicate the sign of rotation. The close configurational relationship between laevorotatory fructose and the dextrorotatory aldohexoses considered above is evident from a comparison of their configurational formulas. This comparison shows that *d*(+)glucose, *d*(+)mannose, and *d*(−)fructose are identical in respect to the configurations of the three asymmetric carbon atoms nearest the CH_2OH group. It is therefore not surprising that each of these sugars on treatment with dilute alkali passes into an equilibrium mixture which contains some of each of all three. This conversion probably proceeds through the ene-diol form common to all three.



Ene-diol of glucose, mannose, fructose

Structure of *d*(−)Fructose. The structural formula of *d*(−) fructose as a ketohexose is established by the following facts. It forms a pentaacetate, and therefore the molecule contains five hydroxyl groups. On reduction it yields a hexahydroxy compound (*d*-sorbitol) with two more hydrogen atoms in the molecule than the original sugar. It is therefore *either* an aldehyde or a ketone. Even on cautious oxidation two carbon atoms are lost, and a monobasic acid is formed. This proves that the compound is a ketone and not an aldehyde, and that the ketonic group is the second group in the chain. (The other oxidation product is glycollic acid, $CH_2OHCOOH$.) The reduction of *d*(−)fructose to the same hexahydroxy compound as was obtained from glucose proves that the same chain is present in both compounds.

d(−)Fructose occurs in many fruits and, together with dextrose, is a product of the hydrolysis of cane sugar. It is best prepared by the hydrolysis of a polysaccharide, **inulin**, which occurs in dahlia tubers and the Jerusalem artichoke.

The Aldopentoses. Of the eight isomeric aldopentoses only three are of general interest. Two are formed by the hydrolysis of polysaccharides of high molecular weight known as *pentosans*. These are ***l*(+)arabinose** and ***d*-xylose.** The pentosans together with similar compounds which yield mannose or galactose on hydrolysis are known as *hemicelluloses*. They occur widely distributed in plants particularly

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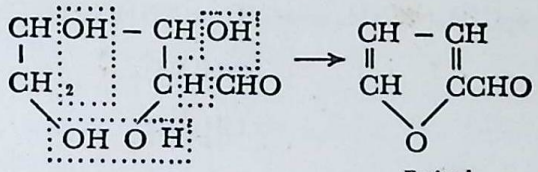
associated with cellulose in cell walls. Cherry gum consists largely of a pentosan which yields *l*(+)arabinose on hydrolysis. *d*-Xylose is obtained by the hydrolysis of straw or bran. The third pentose of importance is ***d*-ribose** which occurs in nucleic acids and in a number of other compounds of interest to the biochemist.

The aldopentoses resemble the aldohexoses closely in most of their reactions. The action of hot hydrochloric or sulfuric acid serves to differentiate the two classes; only the pentoses form a volatile aldehyde known as *furfural*. This substance contains a five-membered ring containing oxygen. Its presence can be established by a number of color reactions. Its formation can be visualized by writing the dehydration of an aldopentose in the following way.



Furfural

REACTIONS OF THE MONOSACCHARIDES

Both the aldoses and the ketoses are oxidized by warm Fehling's solution and warm ammoniacal silver nitrate. This ease of oxidation would be surprising in a ketone, had we not already encountered it with the α-hydroxy ketones (p. 248). The ketoses differ from the aldoses in that the latter, on cautious oxidation with bromine water, yield an acid with the same number of carbon atoms; the ketoses yield acids with fewer atoms. Neither aldoses nor ketoses give the characteristic aldehyde test with Schiff's reagent (p. 144). Both react with phenylhydrazine (p. 143), $C_6H_5NHNH_2$, to form yellow crystalline **osazones** which are less soluble than the sugars. This reaction was discovered by Emil Fischer[1] and is of great value in identifying and purifying the monosaccharides. We have also come across osazone formation earlier: it is a characteristic reaction of α-hydroxy aldehydes and ketones (pp. 248–249).

[1] Emil Fischer (1852–1919). Professor at the University of Berlin; the successor to A. W. von Hofmann (p. 180). His discovery of phenylhydrazine was made in 1875 at Strassburg; it was not until some years later that he applied this reagent to a study of the sugar series. It is largely due to his labors that the relationship of the isomeric pentoses and hexoses was finally established.

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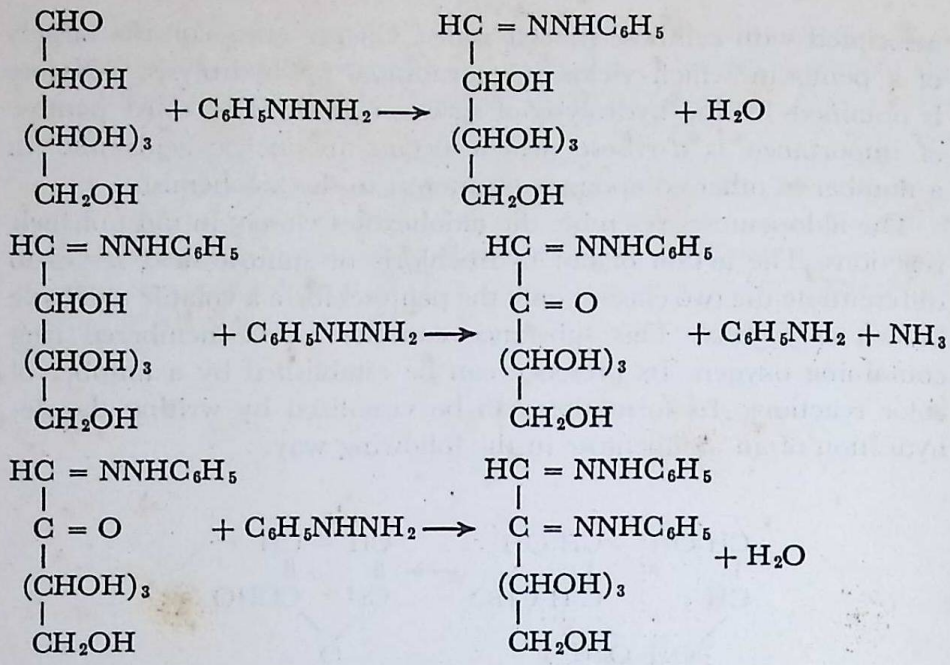
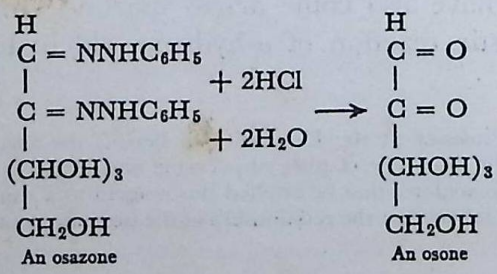


A similar reaction takes place with ketoses, except that here the terminal CH_2OH group next to the CO group is involved in the oxidation. It is possible to isolate the phenylhydrazones before the reaction proceeds further.

Sugars which are identical except for the first two carbon atoms (atoms 1 and 2) will yield the same osazone. Thus, *d*-glucose, *d*-mannose, and *d*(−)fructose when treated with an excess of phenylhydrazine all form the same osazone. This fact is very useful in relating these three substances, since it proves that the configuration of the three asymmetric atoms nearest the CH_2OH group (atoms 3, 4, and 5) is the same in all three compounds.

By means of the osazone we can convert an aldose to a ketose. The osazone is hydrolyzed to an α-ketoaldehyde, an **osone,** by warming with concentrated hydrochloric acid.



An osazone — An osone

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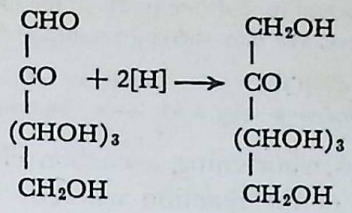
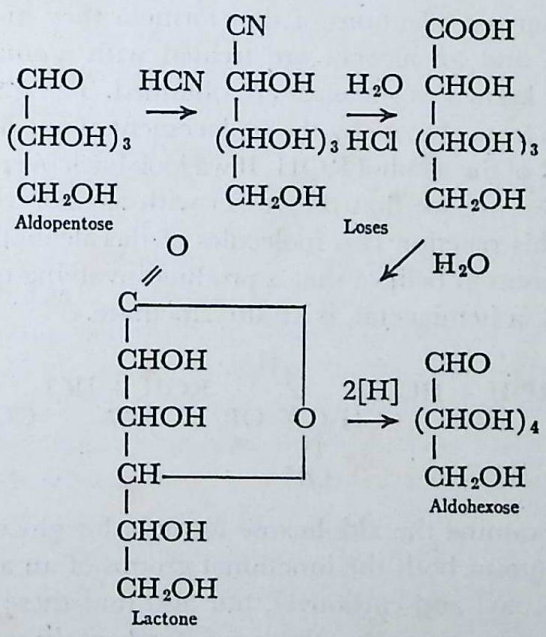
The osone on reduction furnishes a ketose.



Lengthening the Carbon Chain. The carbon chain of an aldose may be lengthened by a series of reactions. This process is very useful as it enables one to prepare hexoses from pentoses, and thus relate the two classes of compounds. The fundamental reactions are (1) the preparation of an α-hydroxy acid by a process we have used before (p. 238), and (2) the reduction of this hydroxy acid to the corresponding aldehyde. This reduction takes place because the hydroxy acid spontaneously forms a lactone which is the substance that undergoes reduction. (Acids, it will be recalled, are not amenable to reduction; but esters are, and a lactone is an ester.) The following equations will illustrate the procedure.



This same set of reactions may be used in converting *a ketose to an aldose*. The ketose is first reduced to the hexahydroxy compound. This is then cautiously oxidized to the acid. This acid (in the form of its lactone) is then reduced to the aldose. The difficulty in this process is that when the hexahydroxy compound is formed it has two points of attack for the oxidizing agent; the oxidation has to be carefully controlled as other-

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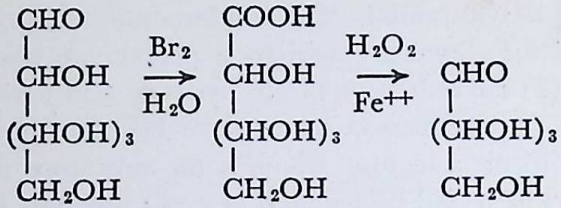
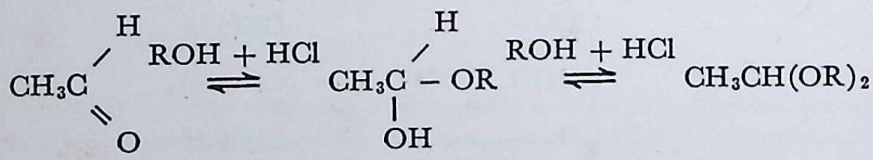
wise a dibasic acid is formed. The names of the polyhydric compounds formed by reducing the sugars always end in *-itol* (see p. 217); the names of the corresponding monobasic acids end in *-onic*. We may therefore summarize the process thus:

$$\text{ketose} \xrightarrow{[H]} \textit{-itol} \xrightarrow{[O]} \textit{-onic}\ \text{acid} \xrightarrow{-H_2O} \text{lactone} \xrightarrow{[H]} \text{aldose.}$$

The reverse process, shortening a carbon chain, can be effected by taking advantage of the reaction whereby an α-hydroxy acid is oxidized to the corresponding aldehyde, water, and carbon dioxide (p. 241). The aldose is first oxidized to the corresponding acid, which is then treated with hydrogen peroxide and a trace of a ferrous salt.



Glucosides. We are now ready to consider the reactions of glucose that are not satisfactorily accounted for by the aldohexose formula and to see what modifications of that formula they make necessary. When glucose and an alcohol are treated with a small amount of acid, products known as *glucosides* are obtained. The glucosides differ in composition from glucose by the replacement of one hydrogen atom by the group R of the alcohol ROH. If we look back over the chemistry of the aldehydes, we see that they react with alcohols to form acetals (p. 142). In this reaction two molecules of the alcohol are involved, but there is reason to believe that a product involving only one molecule of alcohol, a hemiacetal, is an intermediate.



If now we examine the aldohexose formula for glucose we see not only that it contains both the functional groups of an alcohol and an aldehyde (hydroxyl and carbonyl), but also that these groups are in position to react with each other and form a six-membered ring (cf. p. 226). A reaction between a hydroxyl group and the carbonyl group in glucose would lead to a hemiacetal; reaction between this product and alcohol would lead to an acetal, a glucoside.

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The reactions of the glucosides are consistent with their formulation as acetals. They do not reduce Fehling's solution, and they are readily hydrolyzed in acid solution.

All aldoses and ketoses, when treated with an alcohol in the presence of a catalyst, form compounds similar to the glucosides; these are given the general name *glycosides*. In most cases two isomeric forms can be obtained known as the *alpha* and *beta*. These differ in their physical properties, particularly in their rotatory power. These isomers are predicted from the theory of stereoisomerism. There are *five* asymmetric carbon atoms in methyl glucoside. The interaction with the alcohol makes the terminal atom asymmetric; corresponding to this asymmetric atom, there are two stereoisomers. In one, the terminal atom is laevorotatory; in the other, it is dextrorotatory. Although a vast number of the naturally occurring glycosides are glucose derivatives, glycosides of other hexoses and of pentoses are found in plant and animal products.

The Cyclic Structure of Glucose. We have just seen that the existence of two isomeric methyl glucosides is a necessary consequence of the cyclic structure. This fact provides the clue to the explanation of two isomeric forms of glucose itself. These are known as *alpha glucose* and *beta glucose*. The former crystallizes from water as a hydrate, the latter is anhydrous. A freshly prepared aqueous solution of the alpha form has a specific rotation of $+109.6°$; a similar solution of the beta form has a specific rotation of $+20.5°$. On standing, the specific rotation of both solutions slowly changes until a final value of $+52.3°$ is reached. This corresponds to an equilibrium mixture of the two forms. This change is known as *mutarotation*.

The two isomeric forms of glucose are clearly parallel to the two isomeric methyl glucosides discussed above. Alpha and beta glucose correspond respectively to a laevo- and a dextro-rotation of the *terminal* atom. Their existence shows that we must write cyclic structures for the two isomeric forms of glucose itself. The ease with which the two isomers pass into each other is in marked contrast to the stability of the two isomeric methyl glucosides. In glucose the migration of a hydrogen atom can take place as in keto-enol tautomerism. It is probable that both cyclic forms are in equilibrium in solution with a small amount of an open-chain form corresponding to the aldohexose formula for glucose.

$$\alpha \text{ Glucose (cyclic)} \rightleftharpoons \text{open-chain aldehyde} \rightleftharpoons \beta \text{ glucose (cyclic)}$$

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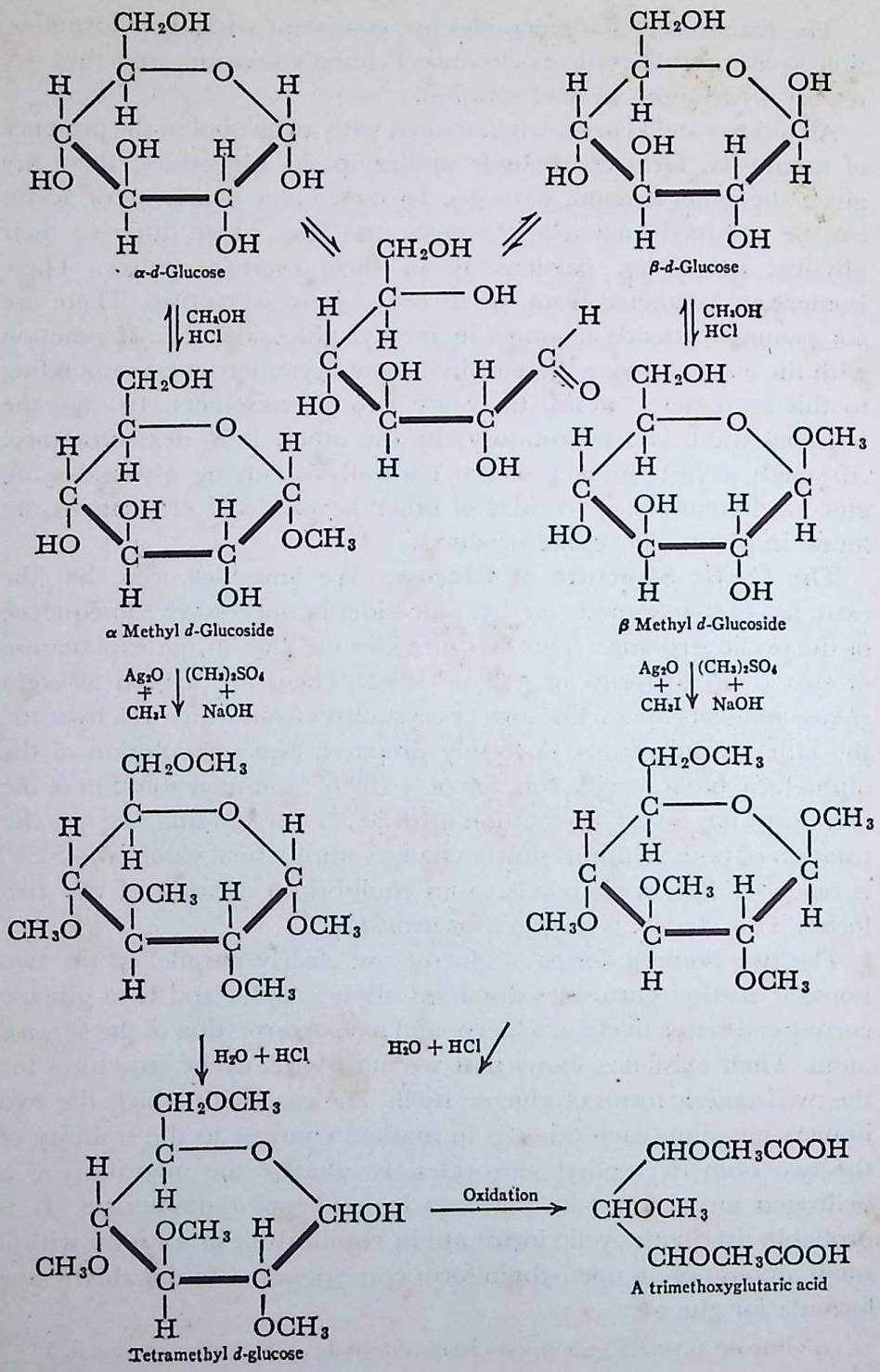

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If we consider the cyclic formula as a general formula for the aldohexoses, it is evident that 2^5 or 32 isomers are predicted in place of the 2^4 or 16 on the basis of the open-chain formula. A careful study has shown the existence of two forms of many aldohexoses corresponding to alpha and beta glucose. Thus, the number of isomeric aldohexoses now known is greater than can be accounted for on the open-chain formula; in time we may expect that all the thirty-two isomers corresponding to the cyclic formula will be prepared.

The Size of the Ring. Even after it became clear that the explanation of the two forms of glucose was to be found in the fact that this substance had a cyclic structure, the size of the ring was uncertain. In the formulas on page 290 a six-membered ring is shown. It is evident that formulas can also be written for analogous cyclic compounds in which smaller or larger rings exist. The determination of the exact ring structure of each sugar derivative marked the most recent stage in the development of the structural chemistry of this class of compounds.

Briefly, the method of determining the ring structure consists in replacing all the hydrogen atoms of the hydroxyl groups by methyl groups and then transforming the resulting methylated sugar to compounds in which the position of the methoxyl groups ($-OCH_3$) could be located. It should be noted that as long as one is dealing with the sugar itself the reversible opening and closing of oxide rings of several sizes is possible. When all hydroxyl groups, except the potential aldehydic group, have been converted into methoxy groups, however, the size of the ring is fixed. From that point on the usual methods of organic chemistry will yield information as to the structure.

The methylation of sugars is carried out by first converting the sugar to the methyl glycoside, treating this compound with silver oxide and methyl iodide or methyl sulfate in alkaline solution. The glycoside methyl group is then removed by hydrolysis with acid. The other methoxy groups being ethers are very resistant to hydrolysis.

Furanose and Pyranose Sugars. The oxidation of the tetramethyl glucose prepared from either α- or β-methyl glucoside yields a trimethoxyglutaric acid. This proves the presence of a six-membered ring in these glucosides. Another methyl glucoside (γ-methyl glucoside) can also be prepared from glucose. It has been shown to contain a *five*-membered ring, since the tetramethyl glucose obtained from this third glucoside by the procedure outlined above did not yield a *tri*methoxy but a *di*methoxy acid (dimethoxysuccinic acid) on oxidation.

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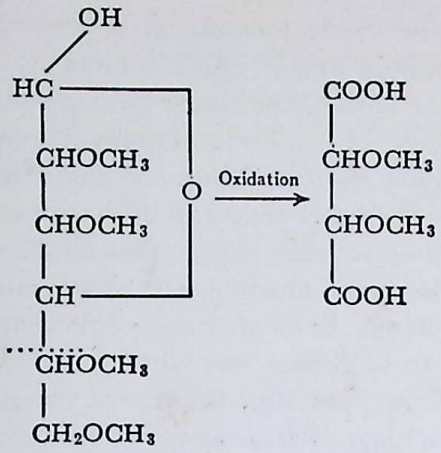
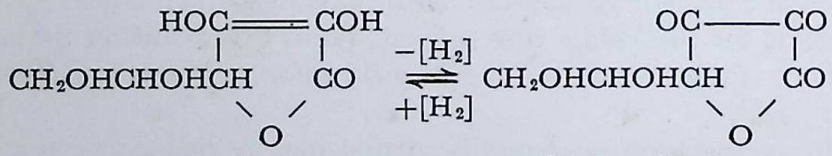


From γ-methyl glucoside — A dimethoxy-succinic acid

Sugars and sugar derivatives which contain six-membered rings are said to be in the *pyranose* form; those which contain a five-membered ring are called *furanose* compounds. The glycosides which are obtained by the usual procedure from the aldohexoses and aldopentoses all contain the pyranose structure. The furanose ring, however, is present in a number of aldoketose derivatives which occur in nature, including cane sugar (see below).

Ascorbic Acid, Vitamin C. Ascorbic acid is present in a great variety of vegetables and in particular in citrus fruits. It is a strong reducing agent, reducing both ammoniacal silver nitrate and Fehling's solution in the cold. This behavior is due to the presence of an **ene-diol** system in the molecule.



Ascorbic acid (Vitamin C) — Dehydroascorbic acid

Ascorbic acid is a sufficiently strong acid to react with sodium carbonate solutions; the acidity is due to one of the hydrogens of the ene-diol system. Since it is also a lactone, it may be opened by treatment with alkali. The absence of ascorbic acid from an otherwise normal diet ultimately leads to scurvy. This vitamin is now manufactured synthetically by a series of reactions which start with *d*-glucose.

DISACCHARIDES

Sucrose or cane sugar, $C_{12}H_{22}O_{11}$, is the most familiar sugar. It is readily hydrolyzed in the presence of a little acid or by the action of

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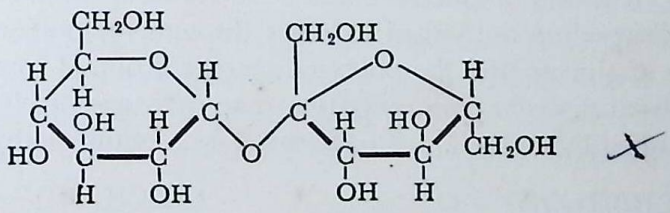
the enzyme **invertase**; the products of hydrolysis are one molecule of glucose and one of fructose.

$$C_{12}H_{22}O_{11} + H_2O \xrightarrow[\text{acid}]{\text{Enzyme or}} \underset{d(-)\text{Fructose}}{C_6H_{12}O_6} + \underset{d\text{-Glucose}}{C_6H_{12}O_6}$$

This reaction is called *inversion* because the mixture of products rotates the plane of polarized light in the opposite direction from pure sucrose, which is dextrorotatory. Since fructose is laevorotatory and glucose dextrorotatory, one might imagine that an equimolar mixture of the two would be inactive. This is not so, however, for the action of fructose is more powerful than that of glucose; a mixture of the two in equal amounts therefore rotates the plane of polarized light to the left. The name *invert sugar* is applied to a mixture of glucose and fructose.

The hydrolysis of sucrose establishes the fact that its molecule is built up of one molecule of glucose and one of fructose joined together with the loss of water. The ease with which the hydrolysis takes place suggests that the nature of the linkage is similar to that in the glucosides. Sucrose does not reduce Fehling's solution. This fact indicates that neither the aldehydic nor ketonic groups of the constituent monosaccharides are free in the disaccharide. The following formula represents the sucrose molecule.



It will be noted that the fructose part of the molecule contains a five-membered ring (furanose form of fructose), the glucose a six-membered ring. This was established by methylation of the disaccharide followed by hydrolysis and determination of the structure of the two methylated hexoses.

Maltose and Lactose. Two other disaccharides are of general interest; they are maltose and lactose. They both crystallize with a molecule of water of crystallization and have the molecular formula $C_{12}H_{22}O_{11}\cdot H_2O$. **Maltose** is the product of the enzymatic hydrolysis of starch. This hydrolysis is the first step in the digestion of starchy foods; the saliva contains an enzyme, **ptyalin,** which rapidly converts starch into maltose. Maltose is the sugar produced by the action of

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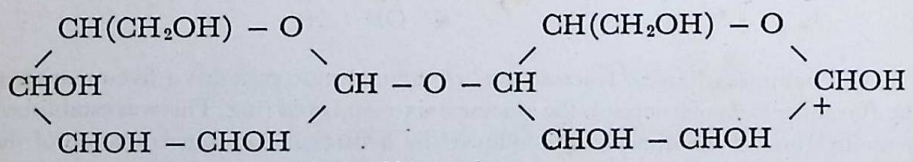
diastase (from malt) on starch, and its biochemical transformation to alcohol was mentioned in the first chapter of this book (p. 14). On hydrolysis maltose yields two molecules of glucose. This hydrolysis to glucose is the first step in the formation of alcohol from maltose. The reaction is brought about by an enzyme present in the yeast. The glucose thus produced is then fermented to alcohol by another enzyme in the yeast cell (zymase).

Lactose is the sugar which occurs in milk. It is present to the extent of about 4 per cent. On hydrolysis it yields a molecule of glucose and one of **galactose.** Lactose is fermented to lactic acid by the lactic acid ferment which is responsible for the souring of milk (p. 239); it is not fermented by ordinary yeast.

Both maltose and lactose are **reducing sugars** like the monosaccharides; that is, they are oxidized by warm Fehling's solution. In this respect they differ from sucrose which has no action on Fehling's solution. The reason for this difference is seen by comparing the formula for sucrose with that for maltose or lactose which is given below. Maltose and lactose both have one of the original aldehydic groups of glucose still free in the molecule (shown by a cross in the cyclic form written below). The free terminal group in maltose or lactose (a potential aldehyde group) confers on these disaccharides all the properties of aldoses. Sucrose, on the other hand, has no such group. It is both a glucoside and a fructoside in which the monosaccharide residues are joined together through the potential aldehydic group of glucose and the potential ketonic group of fructose.

In both disaccharides, only pyranose rings are involved. This was established by methylation and degradation of the methylated sugars.



Maltose or lactose
(In maltose the sugar residue on the left is glucose; in lactose it is the isomeric galactose.)

Enzymatic Hydrolysis of Glucosides. The disaccharides may be regarded as glucosides. This is evident from the formula for maltose written above; one molecule of glucose (written on the right) is in place of the methyl alcohol which has condensed with glucose in the methyl glucosides. It will be recalled that there are two isomeric glucosides possible in each case which we designate as *alpha* or *beta.*

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It has been found that there are enzymes which *specifically* hydrolyze the one form of glucoside or the other. These enzymes act almost independently of the nature of the hydroxy compound condensed with the glucose residue. One of these enzymes is known as *maltase*, because it hydrolyzes this sugar to two molecules of glucose. It occurs widely distributed in nature; for example, in yeast and in the pancreas. It acts on all the glucosides of the one series which are known as the *alpha glucosides*. The other enzyme is known as *emulsin* and hydrolyzes only *beta glucosides*. Both enzymes are very specific and will not act on the glucoside of the other configuration. Once this fact had been established, it was possible to use these enzymes in determining the configuration of a glucoside.

POLYSACCHARIDES

Starch, glycogen (animal starch), and **cellulose** are all substances of high molecular weight which on hydrolysis yield glucose. They may all be represented by the empirical formula $(C_6H_{10}O_5)_x$ or $(C_{12}H_{20}O_{10})_n$. The polysaccharides are either insoluble in water and organic solvents, or form colloidal dispersions which often are jellies. They do not show the aldehydic reactions of monosaccharides; the presence of three hydroxyl groups connected with each group of six carbon atoms is readily demonstrated by acetylation with acetic anhydride.

While the molecules of the three important polysaccharides mentioned above are composed of only glucose molecules joined together, the class includes other types of compounds. For example, inulin is a polysaccharide which on hydrolysis yields the ketohexose, fructose.

CELLULOSE

Common Forms of Cellulose. The structural material of the plant world is largely cellulose. It is the substance present in vegetable fibers and fabrics. Pure filter paper and "cotton wool" are examples of nearly pure cellulose.

In wood the cellulose fibers are embedded in an amorphous material of high molecular weight known as *lignin*. In the manufacture of cellulose from wood, the operations are designed to remove this lignin and hemicellulose (p. 284). The cellulose fibers can be separated from these materials by treatment with such reagents as sodium hydroxide or calcium bisulfite which decompose or dissolve the lignin.

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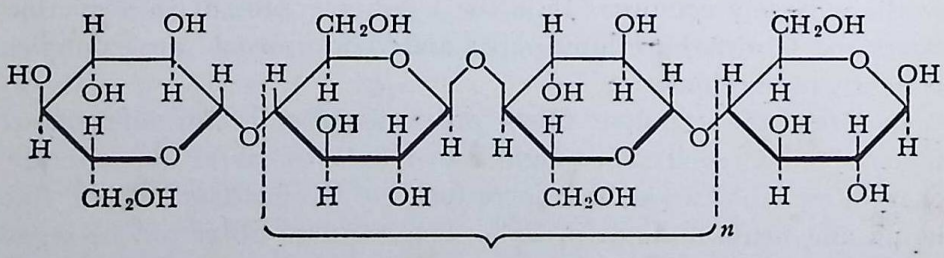
The manufacture of paper from wood consists essentially in separating the cellulose and then matting the fibers together. The cheaper papers are prepared from mechanical pulp which is merely soft wood disintegrated in a stream of water. Lignin and other impurities are present, and their presence can be shown by a yellow coloration with aniline hydrochloride solution.

Properties. Cellulose is insoluble in water and all organic solvents. It dissolves in Schweitzer's reagent (an ammoniacal solution of copper hydroxide), as the result of a chemical reaction. On acidification the cellulose is precipitated.

Cellulose is much more resistant to hydrolysis than starch or glycogen and is attacked only slowly by boiling with dilute acids. Cellulose dissolves in concentrated sulfuric acid; on diluting the solution and boiling it, glucose is formed as the final product.

Chemical Constitution of Cellulose. On careful hydrolysis of cellulose, a disaccharide, cellobiose, is formed. This disaccharide on further hydrolysis yields two molecules of glucose. It has been shown that cellobiose has the same structural formula as maltose (p. 294) except that it is a beta glucoside while maltose is an alpha glucoside. The cellulose molecule is composed of a long chain of cellobiose molecules joined together as shown below. It will be noticed that at the right-hand end of the chain a reducing group (an aldehydic group in the hemiacetal form) is present. This is in accord with two facts: (1) Celluloses which have been treated with strong alkali or oxidizing agents appear to have acidic properties corresponding to one carboxyl group in a very large molecule. (2) On complete methylation of cellulose followed by hydrolysis a small amount of 2,3,4,6-tetramethylglucose is formed in addition to 2,3,6-trimethylglucose. The end group would yield the tetramethylglucose and the amount of tetramethylglucose is a measure of the size of the molecule (though some degradation may have taken place during the methylation).



The value of n in the above formula is estimated as greater than 3000

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for native cellulose; for cotton purified by extracting the fats and treatment with dilute alkali the value is 1000 to 3000; for cellulose in wood pulp it may be as low as a few hundred; and in some cellulose derivatives the number of molecules in the chain may even be as small as 50.

Intermolecular forces (p. 71) between the long-chain cellulose molecules are sufficient to hold the molecules in a fairly definite pattern; thus cellulose fibers show an X-ray pattern characteristic of the crystalline state, have high tensile strength, and are insoluble in water and organic solvents.

Cellulose Nitrates. The hydroxyl groups in the polysaccharides form esters as would be expected. The esters of nitric acid can be formed by the direct action of a mixture of nitric and sulfuric acids on the polysaccharide. The cellulose nitrates which are prepared in this way are substances of very great importance. They are often erroneously called *nitrocellulose*. If the reaction is carried out in such a manner that all the free hydroxyl groups are esterified, the material is known as highly *nitrated cotton* or *gun cotton*. It is used as a high explosive in torpedoes. It has the empirical formula $[C_6H_7O_2(ONO_2)_3]_x$ or $[C_{12}H_{14}O_4(ONO_2)_6]_n$. It should be noted that since the molecular weight of cellulose is unknown we may express the analysis either in terms of a unit of six or twelve carbon atoms.

$$[C_{12}H_{20}O_{10}]_n + n6HNO_3 \longrightarrow [C_{12}H_{14}O_4(ONO_2)_6]_n + n6H_2O$$

The lower nitrates of cotton are called *pyroxylin*. They are important because they are soluble in mixtures of various organic solvents. The partial nitration of cotton is accomplished by careful control of the temperature, the concentration of acid, and the length of time of the action. The nitrated cotton resembles the original cotton in its general appearance. In the process of manufacture it is washed free from acid and finally dried by whirling in a centrifuge. After this treatment it still contains considerable water and in this form is not explosive. The water is usually replaced by soaking in denatured alcohol and the material is again centrifuged. It is shipped without danger when it is moist with alcohol.

Smokeless Powder. When a mixture of gun cotton and the lower nitrates is treated with alcohol and ether, or certain other mixtures of organic solvents, it swells into a jellylike mass. This can be rolled into strips or cords of material which when dry have the consistency of dry gelatine. In the manufacture of smokeless powder, nitrated cotton is "gelatinized" in this way and molded into various shapes and sizes. When

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ignited in the open in small quantities, smokeless powder burns without exploding. When ignited in the absence of air, smokeless powder decomposes utilizing the oxygen which is chemically bound in the solid. The decomposition may be represented by the following equation:

$$[C_{12}H_{14}O_4(ONO_2)_6]_n \longrightarrow n5CO + n7CO_2 + n4H_2 + n3H_2O + n3N_2.$$

Under the confinement obtaining in a gun or rifle, the decomposition is rapid and much heat and gas are evolved. The expanding gases propel the shell from the gun. Since there is no solid residue left by the decomposition of smokeless powder, there is no smoke.

Celluloid and Lacquer Paints. Celluloid is manufactured by gelatinizing pyroxylin with alcohol and heating it with camphor. The product may be molded into a variety of shapes by heating to about 100°. At room temperature it is hard and somewhat brittle. As would be expected from its close relationship to smokeless powder, it is very flammable.

Pyroxylin dissolves in a mixture of ether and alcohol, and the solution is known as *collodion*. This material may be regarded as the forerunner of the lacquer paints which are widely used in the automobile industry. The development of these lacquers has been made possible by the cheap production of the higher alcohols (p. 16) and by the discovery of a method of modifying pyroxylin.

Pyroxylin is modified (i.e., made soluble in mixtures of organic solvents to furnish solutions of low viscosity) by heating it for a considerable time in slightly alkaline solution. Modified pyroxylin in a suitable solvent mixture, together with pigments and other additives, constitutes the modern lacquer paints. Large amounts of such organic solvents as butyl acetate are used in their preparation.

Artificial Silks. The essential difference between the appearance of silk and cotton goods is due to the mechanical structure of the fibers. Silk fibers are long, continuous, smooth tubes, whereas cotton fibers are relatively short and irregular. Silk is a protein (Chap. 19), but this is of little significance. The production of artificial silk from cotton is a matter of changing the mechanical structure of the carbohydrate fiber. This may be done by a variety of methods which are based on the same principle. A solution of cellulose or some cellulose derivative is forced through a very fine hole in such a manner that a continuous thread of solid material is formed. These almost invisible threads are then twisted together and the larger thread woven into cloth which closely resembles silk in its luster. **Rayon** is a name which has been given to artificial silk prepared by certain processes.

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The manufacture of artificial silk is a major industry today. During 1937 about 150,000 tons of rayon were produced in the United States alone and in 1941 about 225,000 tons. Of this 1941 production, about 36 per cent was made by the acetate process and the balance, save for very minor amounts, was made by the viscose process.

In the **viscose process** the cellulose is treated with carbon disulfide and alkali which gives a **cellulose xanthate** in which the group $-\overset{\overset{\displaystyle S}{/\!/}}{C}-SNa$ is joined to one or more hydroxyl groups (p. 348). This cellulose xanthate with a small amount of water forms a thick solution known as *viscose*. This may be converted into threads of cellulose by squirting through a fine orifice into dilute acid which removes the xanthate group. **Cellophane** is the trade name given to thin, transparent sheets of regenerated cellulose prepared by forcing viscose through a narrow slot into the regenerating solution; it is rendered moistureproof by coating with a transparent lacquer.

Cellulose Acetate. The cellulose esters of the organic acids cannot be prepared by direct esterification. It is necessary to use the acid anhydride. By the action of acetic anhydride on cotton in the presence of a little acid, cellulose acetate can be prepared. It has the formula $[C_{12}H_{14}O_4(OCOCH_3)_6]_n$. It is soluble in several organic solvents, particularly the halogen derivatives of the aliphatic hydrocarbons. On partial hydrolysis the material becomes soluble in a wider variety of solvents. Material thus prepared is soluble in acetone, and can be obtained as a strong flexible film or thread by evaporating the solvent. Unlike the cellulose nitrates, cellulose acetate burns with difficulty. For this reason moving-picture films prepared from it may be used without the precautions against fire which are necessary with the ordinary films manufactured from cellulose nitrate. Large quantities of acetic anhydride are manufactured for the use of this industry (pp. 89, 165).

STARCH AND GLYCOGEN

Starch occurs as white granules in nearly all plants. Starch granules from different plants differ greatly in size and shape. The food value of cereals and many other vegetable foods is due primarily to the starch which is present in them. For example, *rice* is about 75 per cent starch, *corn* 50 per cent, and *potatoes* 20 per cent.

Starch is practically insoluble in cold water, but when a suspension

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of starch in water is heated, the granules swell and form a viscous solution which on cooling sets to a jelly. On dilution a colloidal solution of starch can be obtained which is liquid at room temperature. Such a solution shows none of the characteristic reactions of a monosaccharide. If it is boiled with dilute hydrochloric acid, the starch is completely hydrolyzed to glucose. If the enzyme diastase is allowed to act on a suspension or solution of starch, a solution of maltose results. Starch gives a characteristic blue color with iodine; the test is very delicate. Glycogen gives a brown to violet color. Dextrine yields a color with iodine which varies from red to violet, whereas no color is formed when the mono- and disaccharides are treated in the same manner.

Structure of Starch and Glycogen. Naturally occurring substances of high molecular weight are composed of molecules of somewhat different size, though the spread may not be so large as it is with many synthetic polymers. Nevertheless, when we consider the size of the molecules we speak in terms of a range or average molecular weight. The spread of molecular weight of the molecules in starch is very marked. By treatment of starch with hot water it is possible to separate two fractions, apparently without degradation of the original molecules. One fraction (amylose) has a molecular weight of 10,000 to 60,000; the other fraction (amylopectin), which constitutes the major portion of the material, is composed of much larger molecules which have molecular weights from 60,000 to 1,000,000.

Starch differs from cellulose in two respects. Cellulose consists of long chains of glucose residues joined together by beta glucoside links; in starch the glucoside links correspond to alpha glucosides. Furthermore, in amylopectin there appear to be branched chains of glucose units attached to a straight-chain interior unit through the $-CH_2OH$ groups of the chain and the usual alpha glucosidic link. Evidence of this structure has been obtained by studying the effect of certain enzymes which degrade the molecule by hydrolysis in steps. The structure of glycogen appears to be similar to that of amylopectin.

One consequence of the lack of compactness of the starch molecules as compared with those of cellulose is seen in the different behavior of the two materials toward water. The straight chains in cellulose are favorable to a close packing of the molecules in crystal-like fibers where the intermolecular forces are relatively large. Solvent molecules therefore have no effect on cellulose; this is true even of hydroxyl-containing solvents such as water and the alcohols and is true in spite

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of the fact that cellulose is a polyhydroxy compound. The more bulky starch molecules do not form so coherent and rigid a pattern; therefore, starch swells when placed in water and readily forms a colloidal dispersion. Glycogen, in structure and behavior with solvents, resembles starch.

The mechanical properties and solubilities of substances of high molecular weight are the resultant of a number of different effects. A comparison of Polythene, rubber, Nylon, cellulose, and starch (all substances previously encountered in this book) is of interest in this connection. The old rule that like dissolves like has even more validity with large molecules than with small. Rubber swells in hydrocarbon solvents, not with water; some of the polyhydroxy compounds (starches) swell with water and form colloidal solutions, but none interacts with hydrocarbons. The physical properties are determined by intermolecular forces. While these forces are higher with polar groups (amides, Nylon, hydroxy compounds, cellulose, and starch), the shape of the molecule and the ability to pack into coherent patterns are of great importance. While all substances of high molecular weight have very high boiling points and are without exception either crystalline, fibrous, or elastic solids, solubility cannot be so readily generalized. A striking example of this is the behavior of polyvinyl alcohol, a synthetic material of high molecular weight obtained by hydrolysis of the polyvinyl esters (p. 305). Polyvinyl alcohol molecules are composed of straight chains of which a fragment may be represented by $-CHOHCH_2CHOHCH_2CHOHCH_2-$. Although starch, cellulose, and polyvinyl alcohol all contain one hydroxyl group for each two carbon atoms, only polyvinyl alcohol is completely soluble in water. This is attributed to the fact that the intermolecular forces and the shape of the molecule do not give a crystal-like pattern at room temperature. The material may be thought of as like rubber with hydroxyl groups in the molecule; the flexibility of the hydrocarbon chain is very different from that of a string of glucose rings. The intermolecular forces between water molecules and the hydroxyl group entirely overcome the intermolecular forces between the flexible chains in the amorphous solid. We find in the proteins substances of high molecular weight, some of which are soluble in water because the interaction with the solvent molecules is greater than the forces holding the long chains together.

Manufacture of Starch, Glucose, and Dextrine. Starch is usually prepared commercially from corn or potatoes by a mechanical process of grinding and washing. A suspension of impure starch in water is thus obtained; by allowing it to settle slowly, the impurities are deposited first and may be removed. A microscopic examination of starch will reveal the source of the material, as the granules are characteristic of the plant from which they come. Starch is used in laundry work, in cooking, in the manufacture of pastes, and in the preparation of dextrines and glucose.

The hydrolysis of starch to glucose is carried out on a very large manufacturing scale. A few per cent of hydrochloric acid is used as

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the catalyst, and, after the completion of the hydrolysis, this is carefully neutralized. The evaporation of the glucose solution thus prepared yields thick, syrupy solutions, which are widely sold as sweetening materials for domestic use and in the manufacture of candy.

When dry starch is heated to 200° to 250°, a material known as *dextrine* is produced. It is soluble in cold water yielding a syrupy solution which has strong adhesive properties. Dextrine is used in manufacturing the mucilage used on postage stamps. From its behavior, dextrine appears to be a polysaccharide of smaller molecular weight than starch. On hydrolysis it yields glucose. Dextrines are also formed as intermediate compounds in the enzymatic hydrolysis of starch to maltose.

QUESTIONS AND PROBLEMS

1. Write stereochemical formulas for sucrose, maltose, and lactose. Explain with the aid of the formulas why one of these three is a reducing sugar.

2. Point out the differences between the lacquer paints and the paints based on the vegetable oils.

3. Outline the evidence which indicates that glucose is a simple open-chain pentahydroxy aldehyde.

4. What is the meaning of the prefixes *d*- and *l*- and (+) and (−)? Illustrate with examples from carbohydrate chemistry.

5. If a naturally occurring substance is shown to be a glucoside since it furnishes glucose and an alcohol on hydrolysis, how would you determine whether it was an α or β glucoside?

6. How would you determine the size of the ring in the glucoside described in Question 5?

7. What is mutarotation? Show how occurrence of mutarotation and the existence of two isomeric glucosides made it necessary to modify the open-chain structure of glucose.

8. Describe the preparation and use of dextrine and the cellulose nitrates.

9. Outline the reactions you would use to add a carbon atom to or remove a carbon atom from an aldose.

10. Compare, by writing equations for the reactions involved, the chemical behavior of aldohexoses, ketohexoses, and simple aldehydes.

11. What is the structural unit in cellulose? What is the evidence for your statement?

12. Compare the structures of starch and cellulose.

13. Describe the manufacture of rayon.

14. Write structural formulas for an osazone, for Vitamin C, for gluconic and saccharic acids, for sorbitol, and for an osone.

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15. Write equations for the reaction between glyceric aldehyde and phenylhydrazine. Based on this can you suggest a reaction which would show the structural and configurational relation of *d*-mannose to *d*-glucose?

16. Show how you could differentiate by simple methods (*a*) a solution of glucose and of sucrose, (*b*) a hexose and a pentose, (*c*) ascorbic acid and fructose, (*d*) cellulose acetate and cellulose nitrate.

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Chapter 16

UNSATURATED ALCOHOLS, ACIDS, AND CARBONYL COMPOUNDS

The acids, alcohols, aldehydes, and ketones which nave been considered in the previous chapters may be regarded as derivatives of the paraffin hydrocarbons. We shall now consider similar compounds which are derived from the unsaturated hydrocarbons. If the functional group (for example, the carboxyl group) is separated from the unsaturated linkage by two or more carbon atoms, the two reactive portions of the molecule have little influence on each other, and the reactions of the compound are those characteristic of both the functional group and an unsaturated hydrocarbon. If, however, the double linkage is within one or two carbon atoms of the functional group a number of peculiar properties often manifest themselves and give rise to special reactions. Examples of this will be noted particularly in the unsaturated acids and carbonyl compounds.

UNSATURATED ALCOHOLS

Vinyl Alcohol. The simplest imaginable unsaturated alcohol would be that formed by the replacement of one hydrogen atom of ethylene by a hydroxyl group. Such a compound is unknown, but we give to it the name *vinyl alcohol*. The reason for the nonexistence of vinyl alcohol is evident from the discussion of tautomerism in Chap. 14. Vinyl alcohol is the enolic form of acetaldehyde; in all the reactions in which we would expect to obtain it, we find instead acetaldehyde itself.

$$\underset{\text{Vinyl alcohol (unknown)}}{CH_2 = CHOH} \xrightarrow[\text{shift}]{\text{Tautomeric}} CH_3CHO$$

We have already considered the problem of the existence of other enolic compounds which contain the grouping C = COH (p. 264).

Vinyl Halides and Esters. Although vinyl alcohol cannot be prepared, the corresponding halides and esters are stable substances.

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Vinyl bromide is formed by the action of strong potassium hydroxide on ethylene dibromide and is prepared by the action of hydrogen bromide on acetylene.

$$CH_2BrCH_2Br + KOH \longrightarrow CH_2 = CHBr + KBr + H_2O$$
$$CH \equiv CH + HBr \longrightarrow CH_2 = CHBr$$

Vinyl chloride can be prepared by similar reactions. **Vinyl bromide** is a sweet-smelling liquid which boils at 16°. It readily polymerizes under the action of light or certain catalysts, and forms an amorphous mass which is insoluble in all common solvents. In general, compounds containing the vinyl group, $CH_2 = CH$, are very prone to undergo polymerization to compounds of high molecular weight. In this respect the vinyl compounds resemble the dienes (p. 114).

The halogen atom in the vinyl halides is extremely unreactive. In fact, all compounds containing a halogen atom attached to an unsaturated carbon atom ($C = CBr$) differ greatly from the alkyl halides. For example, no reaction occurs when such substances are boiled with water or treated with cold alcoholic potassium hydroxide, sodium methoxide, or potassium cyanide; all these reagents, it will be recalled, readily enter into metathetical reactions with the alkyl halides. It is usually possible to eliminate another molecule of hydrogen halide from the vinyl halides and similar compounds by the action of very strong alkali at a high temperature. In this way an acetylene linkage is formed.

$$CH_2 = CHBr + KOH \xrightarrow{\text{High temperature}} CH \equiv CH + KBr + H_2O$$

The double linkage in vinyl bromide is very similar to the unsaturated linkage in ethylene itself. Thus, the vinyl compounds are readily oxidized, and combine with bromine and hydrobromic acid. The latter reaction takes place in such a way that the bromine goes to the carbon already containing the halogen atom, and ethylidene dibromide is the product.

$$CH_2 = CHBr + HBr \longrightarrow CH_3CHBr_2$$

Vinyl acetate, $CH_2 = CHOCOCH_3$, is prepared industrially from acetylene. Its polymers and those prepared from vinyl chloride are used in connection with the preparation of artificial resins, varnishes, and lacquers. Polymeric vinyl acetate is known in the trade as *Vinylite*.

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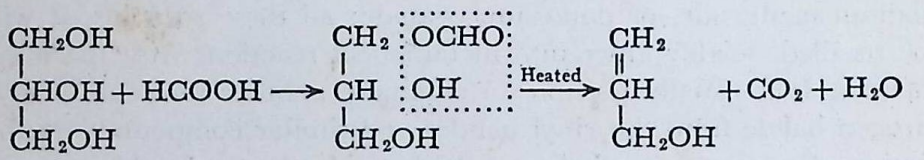
SOME REPRESENTATIVE UNSATURATED ALCOHOLS

Name	*Formula*	*Boiling Point*	*Density at 20°*
Allyl alcohol	$CH_2 = CHCH_2OH$	97°	0.854
Methyl-vinyl-carbinol	$CH_2 = CHCHOHCH_3$	96–97°	—
Allylcarbinol	$CH_2 = CHCH_2CH_2OH$	112–114°	0.848
Vinyl-ethyl-carbinol	$CH_2 = CHCHOHC_2H_5$	114–115°	0.840
Methyl-allyl-carbinol	$CH_2 = CHCH_2CHOHCH_3$	115°	0.834
β-Allyl-ethyl alcohol	$CH_2 = CHCH_2CH_2CH_2OH$	139°	0.863

Allyl Alcohol. The simplest compound in which the hydroxyl group is not directly attached to the double linkage, but on the next carbon atom, is allyl alcohol, $CH_2 = CHCH_2OH$. It is evident that this compound is not an enol, and therefore does not tautomerize to a ketone or aldehyde. Allyl alcohol is prepared by heating glycerol with oxalic acid or formic acid. With the latter, glycerol formate is first formed, which then decomposes on further heating to yield allyl alcohol.



A more modern preparative procedure is based on the replacement of the chlorine atom in allyl chloride by hydroxyl; the allyl chloride is obtained by chlorination of propylene, see p. 58.

$$CH_2 = CHCH_2Cl + HOH \xrightarrow{OH'} CH_2 = CHCH_2OH + HCl$$

The structure of allyl alcohol is established by the fact that on reduction it combines with two hydrogen atoms, yielding normal propyl alcohol.

$$CH_2 = CHCH_2OH + 2[H] \longrightarrow CH_3CH_2CH_2OH$$

This fact proves that the compound has either the structure given above or $CH_3CH = CHOH$. The latter possibility is excluded since allyl alcohol can be shown to be a primary alcohol. Thus, the dibromide of allyl alcohol can be oxidized to α,β-dibromopropionic acid, an acid with the same number of carbon atoms as allyl alcohol.

$$CH_2 = CHCH_2OH \xrightarrow{Br_2} CH_2BrCHBrCH_2OH \xrightarrow{HNO_3} CH_2BrCHBrCOOH$$

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Allyl alcohol forms esters with acids in the usual manner. The ethylenic double linkage also has the usual capacity to combine with a number of other atoms or groups. The addition of hydrogen and of bromine have already been mentioned. Allyl alcohol is a liquid of irritating odor which is miscible with water in all proportions. It boils at 97°.

Allyl Halides. Allyl bromide, allyl iodide, and allyl chloride can be prepared from allyl alcohol by the use of the phosphorus halides or by the action of the halogen acids. Allyl chloride, as has already been mentioned, is obtained from propylene, p. 58. The allyl halides are extremely reactive and enter into all the double decomposition reactions characteristic of the alkyl halides. Indeed, such reactions are much more rapid than with the alkyl halides. For example, in the alkylation of sodium acetoacetic ester, allyl iodide is four times as rapid in its action as methyl iodide and 400 times as fast as isopropyl iodide. In the double decomposition reaction with potassium iodide, which yields the corresponding iodo compounds, allyl chloride is eighty times as reactive as normal butyl chloride. It is very interesting that a double linkage *immediately adjacent* to the carbon atom which holds the halogen has increased the speed of the metathetical reactions. In the vinyl compounds where the halogen is *directly attached* to the unsaturated carbon atom metathetical reactions are so slow as to be inappreciable. These facts illustrate the great influence which a carbon-carbon double bond has on a nearby functional group or reactive atom. In those unsaturated halides in which the double bond is two or more carbons removed from the halogen atom, there is very little, if any, increase or decrease in the speed of the metathetical reactions.

$C=CX$	$C=C-C-X$	$C=C-C-C-X$
Unreactive	More reactive than $CH_{2n+1}X$	Approx. same rate of reaction as $C_nH_{2n+1}X$

Allyl Derivatives in Nature. A number of derivatives of allyl alcohol are found in nature. Allyl sulfide, $(C_3H_5)_2S$ (p. 344), is the chief constituent of oil of garlic, and allyl isothiocyanate, C_3H_5NCS (p. 351) (mustard oil), occurs in the mustard seed in combination with glucose (i.e., as a glucoside).

Nomenclature of Unsaturated Alcohols. The unsaturated alcohols are readily named by the Geneva system. The numbers are assigned so that the carbon atom bearing the hydroxyl group has the smallest number; as usual, the longest chain of carbon atoms carrying the functional group is the basis of the name. The following

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examples will make the method evident:

$\underset{3}{CH_2} = \underset{2}{CH} - \underset{1}{CH_2OH}$	propen-2-ol-1
$(CH_3)_2C = CHCH_2CH_2OH$	4-methylpenten-3-ol-1
$CH_2 = CHCH_2CHOHCH_3$	penten-4-ol-2

UNSATURATED ACIDS

The acids which are derived from the unsaturated hydrocarbons are usually classified according to whether an ethylenic or acetylenic group is present and with regard to the relative position of the carboxyl group. For example, acids which are related to the olefin hydrocarbons and have the general formula $C_nH_{2n-1}COOH$, may be either α,β-unsaturated acids, in which the double bond is adjacent to the carboxyl group, $RCH = CHCOOH$; β,γ-unsaturated acids, $RCH = CHCH_2COOH$; γ,δ-unsaturated acids, etc. Where the double bond is two or more atoms removed from the carboxyl group, it seems to be without influence on the latter, and the reactions of the molecule can be readily predicted. Such acids are the unsaturated acids which have been considered in a previous chapter in connection with the fats (p. 209). We shall now consider a few α,β-unsaturated acids which are prepared by special methods and which have some characteristic properties.

Acrylic Acid. The acid obtained by oxidizing allyl alcohol is acrylic acid. It is the simplest α,β-unsaturated acid.

$$CH_2 = CHCH_2OH + 2Ag_2O \longrightarrow CH_2 = CHCOOH + H_2O + 4Ag$$

Since the double linkage in allyl alcohol is attacked by a number of oxidizing agents, rather special reagents as silver oxide must be employed. A cheaper and more convenient method of preparing acrylic acid is first to form the dibromide, $CH_2BrCHBrCH_2OH$, next oxidize this to the corresponding acid (a reaction which can be carried out with a number of powerful agents, since there is no double bond to interfere), and finally, to remove the two bromine atoms by the action of zinc. This last reaction is exactly analogous to one used in the preparation of ethylene.

$$CH_2 = CHCH_2OH + Br_2 \longrightarrow CH_2BrCHBrCH_2OH \xrightarrow{HNO_3}$$

$$CH_2BrCHBrCOOH \xrightarrow{Zn} CH_2 = CHCOOH$$

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Acrylic acid is a liquid which boils at 141° and solidifies at 12°. It is a slightly stronger acid than acetic acid (the influence of the adjacent double linkage being manifest). It enters into all the reactions characteristic of the organic acids. The double linkage reveals itself by the fact that acrylic acid combines with nascent hydrogen, bromine, and hydrobromic acid.

$$CH_2 = CHCOOH + 2[H] \longrightarrow CH_3CH_2COOH$$
$$CH_2 = CHCOOH + Br_2 \longrightarrow CH_2BrCHBrCOOH$$
$$CH_2 = CHCOOH + HBr \longrightarrow CH_2BrCH_2COOH$$

The first reaction serves to establish the structure of acrylic acid, since the reduction product, propionic acid, is a substance of known structure. Not only can this reduction be accomplished catalytically, but it may also be done by the use of sodium amalgam. This fact is of particular interest as ethylene is not affected by sodium amalgam. The reaction with hydrobromic acid has been already mentioned (p. 235). It was noted that the bromine attached itself to the beta carbon atom (furthest from the carboxyl group). *With α,β-unsaturated acids, the halogen atom always unites with the beta carbon atom.* A probable explanation of this mode of addition of the hydrogen halides to the α,β-unsaturated acids will be discussed in connection with the reactions of the unsaturated aldehydes and ketones (p. 320).

Acrylic Esters. Acrylic esters and α-methyl acrylic esters, $CH_2 = C(CH_3)COOR$, deserve special mention since they are readily polymerized by light, heat, and peroxides. By carefully controlling this reaction, clear, colorless resins are obtained which are known as *acryloids*. These resins have excellent optical properties and can be molded into lenses, prisms, and sheets which are used to make laminated safety glass.

Industrially, acrylic esters are prepared from ethylene chlorohydrin which, as we have seen (p. 199), is readily available from petroleum.

$$CH_2OHCH_2Cl + NaCN \longrightarrow CH_2OHCH_2CN + NaCl$$
$$CH_2OHCH_2CN + ROH + H_2SO_4 \longrightarrow CH_2 = CHCOOR + NH_4HSO_4$$

These esters can also be prepared by the dehydration of the esters of lactic acid. The acetates of the lactic esters are dehydrated.

$$\begin{array}{l} CH_3CHCOOR \\ \quad\;\; | \\ \quad\;\; OCOCH_3 \end{array} \longrightarrow CH_2 = CHCOOR + CH_3COOH$$

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Acrylic esters having a methyl group in the alpha position, $CH_2 = C(CH_3)COOR$, are prepared from acetone cyanohydrin by simultaneous esterification and dehydration.

$$CH_3\underset{\underset{OH}{|}}{C}(CH_3)CN + ROH + H_2SO_4 \longrightarrow CH_2 = C(CH_3)COOR + NH_4HSO_4$$

The Crotonic Acids. Crotonic acid, $CH_3CH = CHCOOH$, is another α,β-unsaturated acid. It is very similar in its chemical properties to acrylic acid. It may be prepared by methods outlined above for the preparation of α,β-unsaturated acids and, in addition, by a convenient reaction from acetaldehyde. Acetaldehyde and malonic acid, when heated in glacial acetic acid solution at 100°, condense to form an unsaturated dibasic acid, which at this temperature loses carbon dioxide forming crotonic acid.

$$CH_3CHO + CH_2(COOH)_2 \xrightarrow{100^\circ} CH_3CH = C(COOH)_2 \longrightarrow CH_3CH = CHCOOH + CO_2$$

Similar condensation reactions between other aldehydes and malonic acid offer a convenient general method of preparing α,β-unsaturated acids, $RCH = CHCOOH$, from aldehydes.

Other Methods of Preparing α,β-Unsaturated Acids. Still another method of preparing α,β-unsaturated acids is illustrated by the procedure often used for preparing crotonic acid. This consists in heating the ester of α-bromobutyric acid with a tertiary amine (diethylaniline, $C_6H_5N(C_2H_5)_2$). It is difficult to eliminate hydrobromic acid from an α-bromo acid (as contrasted to a β-bromo acid), but the process can be carried out if the esters are employed.

$$CH_3CH_2CHBrCOOC_2H_5 \xrightarrow[\text{Heated with a tertiary amine}]{-HBr} CH_3CH = CHCOOC_2H_5$$

α,β-Unsaturated acids cannot be prepared from α-hydroxy acids, such as lactic acid, because under the conditions of dehydration lactides result (p. 240). However, it is possible to dehydrate the corresponding nitriles and, in certain instances, the corresponding esters. On the other hand, β-hydroxy acids, which can be prepared by the Reformatsky reaction (p. 237), are generally dehydrated by strong acids to α,β-unsaturated acids. This constitutes another general method of preparing this class of substances.

Isomeric Crotonic Acids. Crotonic acid occurs in two isomeric forms. The explanation of this isomerism will be considered shortly. **Crotonic acid** itself is a crystalline solid melting at 72° and boiling at 189°. It is fairly soluble in water. The isomer, **isocrotonic acid,**

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melts at 15.5° and boils at 169°. On heating isocrotonic acid to 100°, it partly rearranges into the higher melting isomer. The rearrangement is accelerated by traces of iodine or acid or by exposure of a solution of isocrotonic acid to sunlight. In their chemical behavior these two acids are identical, and the same structural formula must be assigned to them. Both are readily reduced by the action of sodium amalgam or by catalytic hydrogenation to *n*-butyric acid. This fact establishes the carbon skeleton, and only the position of the double linkage remains in question. Both acids combine with hydrogen iodide to give the same β-iodobutyric acid. Ozonization followed by decomposition of the ozonides transforms *both* acids into a mixture of acetaldehyde and glyoxylic acid. This is conclusive evidence that crotonic and isocrotonic acids both must be represented by the structural formula $CH_3CH = CHCOOH$.

$$CH_3CH = CHCOOH + O_3 \longrightarrow \text{Ozonide} \xrightarrow{H_2O} CH_3CHO + CHOCOOH + \underset{\text{Removed by a mild reducing agent}}{H_2O_2}$$

Vinylacetic Acid. The simplest β,γ-unsaturated acid is vinylacetic acid, $CH_2 = CHCH_2COOH$. It can be obtained by treating the Grignard reagent formed from allyl bromide with carbon dioxide. There is great difficulty in the preparation of the Grignard reagent from the allyl halides, since they are prone to undergo the Wurtz reaction (p. 41) when treated with magnesium, forming a compound known as *diallyl*, $CH_2 = CHCH_2CH_2CH = CH_2$. This fact again illustrates the enhanced reactivity of allyl halides.

$$CH_2 = CHCH_2MgBr + CO_2 \longrightarrow CH_2 = CHCH_2COOMgBr \xrightarrow{HCl} CH_2 = CHCH_2COOH$$

Vinylacetic acid is reduced to butyric acid and combines with bromine to yield β,γ-dibromobutyric acid.

$$CH_2 = CHCH_2COOH + Br_2 \longrightarrow CH_2BrCHBrCH_2COOH$$

Vinylacetic acid rearranges into the isomeric crotonic acid when it is boiled with alkali; this reaction is reversible and proceeds to a definite equilibrium.

$$CH_2 = CHCH_2COOH \underset{100°}{\overset{\text{Alkali}}{\rightleftharpoons}} CH_3CH = CHCOOH$$

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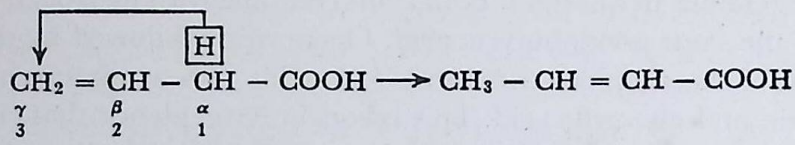
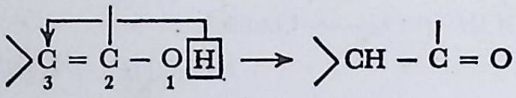
Because of this transformation, vinylacetic acid is not prepared by alkaline hydrolysis of the corresponding nitrile. The nitrile, allyl cyanide, is readily prepared by the action of potassium or cuprous cyanide on allyl chloride. On acid hydrolysis, allyl cyanide furnishes vinylacetic acid.

It is interesting to note that the shift of the double linkage involved in the change from vinylacetic acid to crotonic acid involves a shift of the hydrogen atom from the alpha carbon atom to the gamma carbon atom.

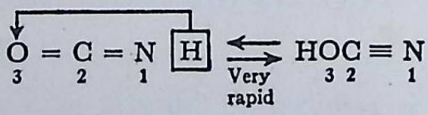


This shift through a three-atom system is similar to the shift of a hydrogen atom involved in the change from an enol to a ketone.



In the three-*carbon* system (no oxygen atom is involved), such a shift occurs only slowly even under the influence of such reagents as boiling sodium hydroxide; on the other hand, the speed of enolization and ketonization is very great even in the presence of but a trace of catalyst. The three-atom system containing an oxygen atom is more *mobile* than the carbon system. In both systems, however, we are dealing with a truly reversible reaction. Although in crotonic acid, the α, β form is present at equilibrium to the extent of 98 per cent, with certain alkyl derivatives the β, γ form predominates in the equilibrium mixture.

An unsaturated three-atom system is present in cyanic acid (p. 333), but it contains a nitrogen atom also. One is tempted to postulate that the mobility is so great in this system that no catalyst is needed and the tautomers (isomers) cannot be isolated; this explanation accords well with the behavior of cyanic acid.



Nomenclature of Unsaturated Acids. Unsaturated acids can be named by a variety of procedures. The position of the double bond may be indicated by Greek letters, and the symbol Δ. Thus, crotonic acid, $CH_3CH = CHCOOH$, is butenoic acid $\Delta^{\alpha,\beta}$, while vinylacetic acid, $CH_2 = CHCH_2COOH$, is butenoic acid $\Delta^{\beta,\gamma}$. The unsaturated hydrocarbon, in this case butene, is the basis for the name which should correspond to the longest carbon chain.

According to the Geneva system, the position of the double bond

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is indicated by a number placed in the name immediately after the "en"; the numbering always starts with the carbon atom of the carboxyl group. Thus, $CH_3CH = CHCOOH$ is called *buten-2-oic acid* and $\overset{4}{CH_2} = \overset{3}{C}H\overset{2}{C}H_2\overset{1}{C}OOH$ is *buten-3-oic acid*. As an application of the Geneva system to complicated unsaturated acids, the following examples may be cited:

$$CH_3CH = \underset{\underset{CH_3}{|}}{C}CH_2CH_2COOH$$

4-methylhexen-4-oic acid;

$$(CH_3)_2C = CH - CH = CH - COOH,$$

5-methylhexadien-2, 4-oic acid.

Fumaric and Maleic Acids. These two isomeric unsaturated dibasic acids are of the greatest interest and importance. They are both represented by the same structural formula.

$$HOOCCH = CHCOOH$$

Fumaric acid occurs widely distributed in nature and is found in small quantities in many plants. It may be prepared by the action of alkali on bromosuccinic acid (which is obtained by brominating succinic acid).

$$\begin{array}{l} CHBrCOOH \\ | \\ CH_2COOH \end{array} \xrightarrow{KOH} \begin{array}{l} CHCOOH \\ \| \\ CHCOOH \end{array} + KBr + H_2O$$

It is also formed by heating *malic acid* (α-hydroxy succinic acid) (p. 240).

$$\underset{\text{Malic acid}}{\begin{array}{l} CHOHCOOH \\ | \\ CH_2COOH \end{array}} \xrightarrow{145^\circ} \underset{\text{Mixture of fumaric and maleic acids}}{\begin{array}{l} CHCOOH \\ \| \\ CHCOOH \end{array}}$$

Maleic anhydride and fumaric acid are prepared industrially by the *catalytic oxidation of benzene*, C_6H_6 (p. 402), by air at 400° to 500°. The properties of fumaric and maleic acids are given below in the table.

The two acids differ strikingly in their physical properties and in their tendency to lose water. Maleic acid readily forms an anhydride when heated by itself or in the presence of a dehydrating agent thereby resembling succinic acid (p. 226). Fumaric acid does not form an anhydride, but when it is heated to a very high temperature maleic

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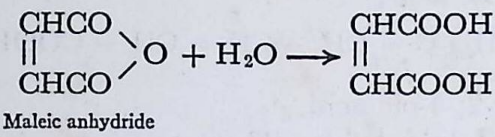
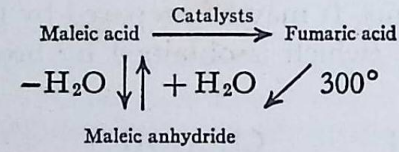
PHYSICAL PROPERTIES OF MALEIC AND FUMARIC ACIDS

	Melting Point	*Solubility in 100 ml H_2O at 18°*	K_A (*18°*)	*Heat of Combustion (Kg-Cal)*
Maleic acid	130°	Very soluble	13×10^{-3}	326.9
Fumaric acid	287°	.445	1.1×10^{-3}	320.1

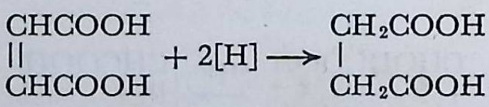
anhydride is formed. **Maleic anhydride** on treating with water slowly yields maleic acid.



Maleic acid is readily converted into fumaric acid by the catalytic action of warm acids, halogens, or sunlight. The reaction is exothermic by about 6 kg-cal and runs essentially to completion, K = *ca.* 10^6 The following diagram illustrates the relationship of the two isomers.



The structures of maleic and fumaric acids are readily established by the fact that on reduction both yield succinic acid.



Both maleic and fumaric acids combine with hydrobromic acid to give the same bromosuccinic acid, and both can be converted into malic acid by heating with water and a catalyst. They are oxidized by permanganate and combine with bromine, though the latter reaction is much slower than with most derivatives of ethylene.

Reaction of Maleic Anhydride with Dienes. Maleic anhydride readily combines with 1,3-dienes (p. 68) to give a ring compound. The reaction with butadiene, for example, is as follows.

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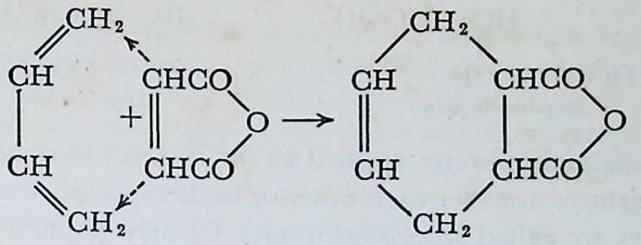

This reaction is general for the system C = C − C = C and is often used to determine whether a new compound has a conjugated system of double bonds. It is a striking demonstration of the capacity of a conjugated system to combine in the 1,4 position. While maleic anhydride is one of the most convenient and useful addends in this type of reaction, many other ethylenic compounds will add to 1,3-dienes. Usually the ethylenic linkage in the addend is in the α,β-position to a carbonyl group, but this is not essential. The addition reaction is known as the **diene synthesis** (see p. 566 and 577).

GEOMETRICAL ISOMERISM

We have seen that there are two crotonic acids, both of which have the same structural formula, and that maleic and fumaric acids are another pair of isomers whose existence cannot be explained in terms of the simple structural theory. In these instances we are not dealing with optical isomers since none of these compounds is optically active, and there are no asymmetrical carbon atoms in the molecule. With the aid of the tetrahedral model of a carbon atom, however, a very satisfactory explanation of the isomerism of these unsaturated compounds can be formulated. A double linkage must be represented with the models by the union of two tetrahedra along one edge. This is shown in the accompanying diagrams. It is clear from an inspection of these diagrams (or better by handling the models themselves) that it is not possible for the two carbon atoms which are joined by a double bond to rotate freely about each other. The double bond is a rigid union of the two atoms. If now the two carbon atoms involved in the double bond carry two different groups, two arrangements are possible depending on whether certain groups are over each other or away from each other. These two spatial arrangements correspond to the two isomers. Thus, maleic acid and fumaric acid are represented by the models shown in Fig. 13. They are represented in a plane as follows.

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```
   HC – COOH                HC – COOH
    ||                       ||
HOOC – CH                   HC – COOH
```

Fumaric acid (trans) Maleic acid (cis)

The names *cis* and *trans* are applied to the isomers to denote whether the similar groups are over each other or in the opposite configuration. Such isomers are called *geometrical isomers*. Clearly geometrical isomerism is a branch of stereoisomerism.

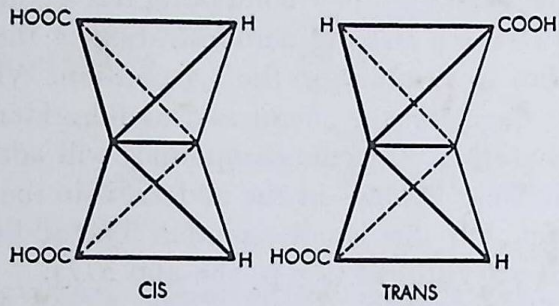

FIG. 13. Diagram of models of maleic and fumaric acids.

The fact that maleic acid readily forms an anhydride is taken as evidence that it corresponds to the *cis* form. The construction of models shows that two carboxyl groups adjacent to each other in space could readily lose water to form a cyclic anhydride. On the other hand, the two carboxyl groups which are in the *trans* position could not. It has not been possible, as yet, to determine definitely which of the isomeric crotonic acids is *cis* and which *trans*. There is no simple reaction such as anhydride formation to serve as an indicator of the configuration.

```
CH3CH                    CH3CH
  ||                       ||
HOOCCH                   HCCOOH
```

The isomeric crotonic acids

In general, it is evident that geometrical isomers may be expected only if both unsaturated carbon atoms carry two different atoms or groups. Thus, compounds of the general type

```
  a     d
   \   /
    C = C
   /   \
  b     d
```

will not have geometrical isomers since the two groups on one carbon atom are the same, and two different spatial arrangements are not possible.

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This isomerism of unsaturated compounds, as we have seen, is due to a restricted rotation of two carbon atoms joined by a double bond. On the other hand, two carbon atoms are free to rotate around a single bond. If this were not so, isomers would be found with such saturated compounds as succinic acid. It is a remarkable fact that the simple assumption, that there is free rotation where the models show it to be possible and restricted rotation where they show it to be impossible, corresponds to the actual experimental facts. The shortening of the distance between the atoms in a double linkage (p. 51) corresponds to a greater binding force and along with this comes also restricted rotation, as the existence of geometrical isomers demonstrates. On the other hand, the conversion of one geometrical isomer into the other (e.g., maleic to fumaric) shows that the restriction on the rotation may be overcome. This isomerization may be imagined as being the opening of one linkage of the two bonds followed by rotation of the atoms around the remaining bond.

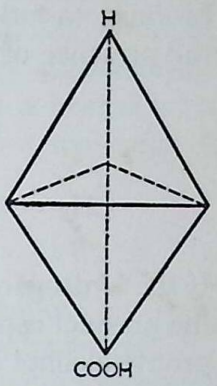

FIG. 14. Diagram of model of propiolic acid.

Acetylenic Compounds. If a model is made of the acetylenic linkage it is clear that no isomers would be predicted. This is illustrated in Fig. 14. Such a prediction is in entire accord with the facts. **Propiolic acid,** $CH \equiv CCOOH$, which can be prepared from sodium acetylene and carbon dioxide, exists in only one form.

$$CH \equiv CH + Na \longrightarrow CH \equiv CNa \xrightarrow{CO_2} CH \equiv CCOONa \xrightarrow{HCl} CH \equiv CCOOH$$

The same is true of other acetylene compounds.

UNSATURATED ALDEHYDES AND KETONES

Acrolein. The simplest unsaturated aldehyde is acrolein or acrylic aldehyde, $CH_2 = CHCHO$. It is a colorless liquid (bp 57°) with an extremely powerful and irritating odor. It may be formed by the careful oxidation of allyl alcohol, but is usually prepared by the dehydration of glycerol. This can be done by heating glycerol with potassium acid sulfate; the unsaturated aldehyde being volatile is collected as a distillate.

$$CH_2OHCHOHCH_2OH \xrightarrow[200°]{KHSO_4} CH_2 = CHCHO + 2H_2O$$

Acrolein is formed in small amounts when glycerides (fats) are heated to a high temperature. The irritating vapors of acrolein are sometimes noticed when fats are heated or burned.

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Acrolein gives the reactions of both aldehydes and olefins. As an aldehyde it can be oxidized to the corresponding acid (it reduces ammoniacal silver nitrate); it reacts with the Grignard reagent to give the corresponding unsaturated alcohol. The presence of the ethylene linkage is demonstrated by the fact that the compound adds bromine to form a dibromide and further by the hydrogenation (in the presence of a platinum catalyst) to propionaldehyde.

$$CH_2 = CHCHO \xrightarrow{Ag_2O} CH_2 = CHCOOH$$

$$CH_2 = CHCHO \xrightarrow[\text{Catalyst}]{H_2} CH_3CH_2CHO \xrightarrow[\text{Catalyst}]{H_2} CH_3CH_2CH_2OH$$

If the hydrogenation is stopped after 1 mole of hydrogen is absorbed, the product is predominantly propionaldehyde. On further reduction, propyl alcohol is obtained.

The structure of acrolein follows from these various reactions which serve to demonstrate (1) the presence of an aldehyde group, (2) a three-carbon chain, and (3) the presence of a double linkage.

PHYSICAL PROPERTIES OF SOME UNSATURATED ALDEHYDES

Name	*Formula*	*Boiling Point*	*Density at 20°*	*Solubility Grams per 100 Grams of Water*
Acrolein	$CH_2 = CHCHO$	52.5°	0.841	About 40
Crotonaldehyde	$CH_3CH = CHCHO$	104.5°	0.847	—
α,β-Dimethylacrolein	$CH_3CH = CCHO$ (with CH_3)	115–119°	0.87	2
α-Methyl-β-ethylacrolein	$C_2H_5CH = CCHO$ (with CH_3)	137°	0.857	Very small

Polymerization of Acrolein. Like many other substances containing the vinyl group ($CH_2 = CH -$), acrolein readily polymerizes forming substances of high molecular weight. This polymerization takes place so readily with acrolein that it is very difficult to store the material unless certain substances are added as stabilizers. The polymerization of acrolein and other unsaturated substances is usually

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catalyzed by the presence of small amounts of peroxide, which are slowly formed by the action of the oxygen of the air. Substances which will react with the peroxides and destroy them prevent the polymerization. Such substances are called *antioxidants*.

Crotonaldehyde. Crotonaldehyde or crotonic aldehyde, $CH_3CH = CHCHO$, is the next higher homolog in the series of α,β-unsaturated aldehydes. It is readily prepared from acetaldehyde through the aldol condensation (p. 137). When aldol is heated with dilute acids or certain other catalysts it readily loses a molecule of water, forming crotonaldehyde.

$$2CH_3CHO \overset{\text{Dil. alkali}}{\rightleftarrows} CH_3CHOHCH_2CHO \overset{\text{Acid}}{\longrightarrow} CH_3CH = CHCHO$$

Crotonaldehyde is a liquid which boils at 105°. Its reactions are very similar to those of acrolein, except that it cannot be polymerized.

α,β-Unsaturated Ketones. A great number of α,β-unsaturated ketones are known since they may be readily prepared by the condensation of ketones and aldehydes. One of the simplest is **mesityl oxide.** It is formed by heating diacetone alcohol (p. 138) with a trace of acid or iodine. These reagents cause an almost quantitative dehydration of the hydroxy ketone with the formation of an unsaturated ketone.

$$2CH_3COCH_3 \overset{Ba(OH)_2}{\rightleftarrows} \underset{\text{Diacetone alcohol}}{(CH_3)_2COHCH_2COCH_3} \overset{\text{Acids}}{\underset{100^\circ}{\longrightarrow}} \underset{\text{Mesityl oxide}}{(CH_3)_2C = CHCOCH_3}$$

It is also possible to obtain mesityl oxide directly from acetone by the action of acids; the yields are very poor, however. Undoubtedly in this reaction diacetone alcohol is first formed which then undergoes dehydration. When this method of preparing mesityl oxide is used, another unsaturated ketone, **phorone,** $(CH_3)_2C = CHCOCH = C(CH_3)_2$, is also formed. Mesityl oxide is a colorless liquid with a peppermint odor. Phorone is a solid which melts at 28°. The boiling points of these and certain other unsaturated ketones are given in the table. Both these compounds on boiling with dilute alkali undergo cleavage with the regeneration of acetone. This is the reversal of the method by which they are formed. Undoubtedly the first step is the addition of water to the unsaturated linkage (or linkages) and the formation of the hydroxyl compound which then undergoes the reversal of the aldol condensation forming acetone.

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PHYSICAL PROPERTIES OF SOME UNSATURATED KETONES

Name	*Formula*	*Boiling Point*	*Density at 20°*
Methyl vinyl ketone	$CH_2 = CHCOCH_3$	80°	0.864
Ethyl vinyl ketone	$CH_2 = CHCOC_2H_5$	38° (68 mm)	
Ethylidene acetone	$CH_3COCH = CHCH_3$	125–128°	0.862
Allylacetone	$CH_2 = CHCH_2CH_2COCH_3$	129°	
Mesityl oxide	$(CH_3)_2C = CHCOCH_3$	130°	0.865
Phorone	$(CH_3)_2C = CHCOCH = C(CH_3)_2$	200°	0.885

Characteristic Reactions of α, β-Unsaturated Carbonyl Compounds. The α, β-unsaturated aldehydes and ketones, since they contain a double bond immediately adjacent to the carbonyl group, have a number of special reactions. These could not be predicted from a knowledge of the characteristics of the carbon-carbon double bond and the carbon-oxygen double linkage. As the first example of the peculiar reactions, we may mention the fact that all α,β-unsaturated ketones and aldehydes combine with halogen acids in such a way that the halogen atom attaches itself to the beta carbon atom. Thus, acrolein combines with hydrogen bromide as follows.

$$CH_2 = CHCHO + HBr \longrightarrow CH_2BrCH_2CHO$$

(A similar situation was encountered with the α,β-unsaturated acids and is also true of their esters.)

A much more striking peculiarity of α,β-unsaturated aldehydes and ketones is the fact that the carbon-carbon double linkage appears to combine with reagents which would be expected to attack only the carbonyl group. For example, when acrolein is treated with sodium bisulfite two moles of the reagent add to the substance, one going normally to the carbonyl group and the other combining with the ethylene linkage.

$$CH_2 = CHCHO + 2NaHSO_3 \longrightarrow \underset{SO_3Na}{\underset{|}{CH_2}}\underset{SO_3Na}{\underset{|}{CH_2}}CHOH$$

Hydrocyanic acid and hydroxylamine also often combine with the ethylenic linkage of α,β-unsaturated ketones and aldehydes. The reaction between mesityl oxide and hydroxylamine may be used as an illustration. When these two substances are allowed to interact at room temperature two different products are formed; one of these is

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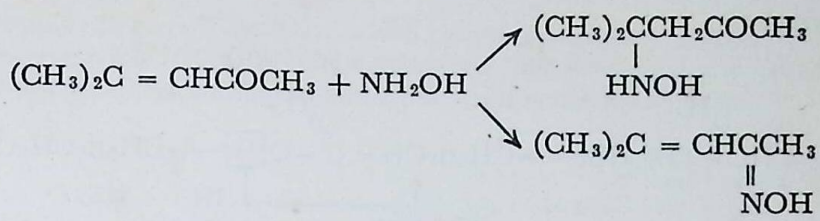
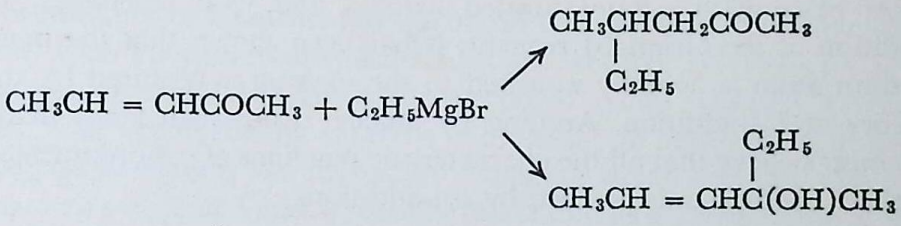
the normal oxime and the other is the compound formed by addition of hydroxylamine to the ethylenic linkage.



The reaction between the Grignard reagent and α,β-unsaturated carbonyl compounds also may take an abnormal course. For example, the action of ethylmagnesium bromide on ethylidene acetone gives the two following products.



In one of these cases the Grignard reagent has apparently added to the carbon-carbon double linkage. It should be noted that such reagents as hydrocyanic acid, hydroxylamine, sodium bisulfite, and the Grignard reagent do not add to ethylenic hydrocarbons, nor do they add to the carbon double linkage in unsaturated aldehydes or ketones *unless this linkage is in the alpha, beta position.*

Conjugated Systems of Double Bonds. Two explanations have been offered for the peculiar reactions of α,β-unsaturated carbonyl compounds. On the one hand, it may be said that the carbon-carbon double bond has been made more active by the presence of the adjacent carbonyl group and will therefore combine with a number of reagents for which it otherwise has no affinity. The two carbon atoms of the double bond are under different influences and the reagent always adds in such a manner that the hydrogen atom attaches itself to the carbon immediately adjacent to the carbonyl group.

An entirely different explanation was offered by Johannes Thiele[1] in 1899, and is supported by a number of experimental facts. He supposed that the actual addition took place in such a way that the hydrogen atom of the reagent combined with the oxygen, and the rest of the reagent combined with the carbon atom. The first product

[1] Johannes Thiele (1865–1918). Professor at the University of Strassburg.

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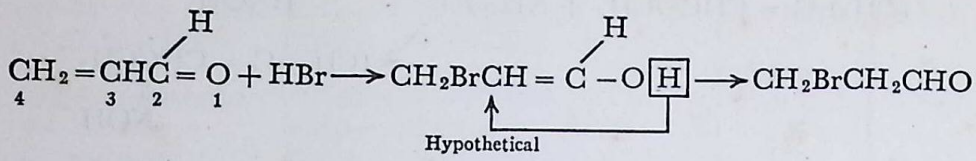
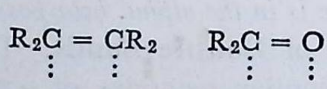
then tautomerized to the final ketone or aldehyde. This mechanism may be illustrated by the addition of hydrobromic acid to acrolein as follows:

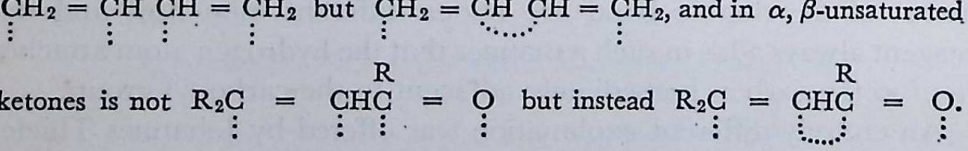


It will be recognized that in the first step of this mechanism a reaction is involved analogous to the 1,4-addition of the dienes (p. 69). In only a few reactions has it been possible to prove that 1,4-addition takes place with α,β-unsaturated ketones and with aldehydes. In addition of the Grignard reagent, it has been shown that the magnesium atom is actually attached to the oxygen as required by the theory of 1,4-addition. Arguing by analogy from such facts, many chemists believe that all the characteristic reactions of α,β-unsaturated carbonyl compounds proceed by 1,4-addition.

Theory of Partial Valence. For its historical interest the theory proposed by Thiele to account for 1,4-addition should be mentioned. In the following diagram the dotted lines represent what Thiele called *partial valences*, a concept for which it is difficult to form a satisfactory physical picture. In a normal double linkage the partial valences are free and serve to attract the usual reagents.



In a conjugated system, however, the adjacent partial valences are mutually satisfied, and the free partial valences only occur at the ends of the system (1,4 positions); thus, the conjugated system in butadiene is not



Additions therefore occur in the 1,4 position.

It must be emphasized that while conjugated systems have the possibility of 1,4-addition and often manifest this possibility, they also take part in many reactions in which each individual double linkage reacts in a normal way. Such reactions are often spoken of as 1,2-*additions*. For example, the combination of acrolein with bro-

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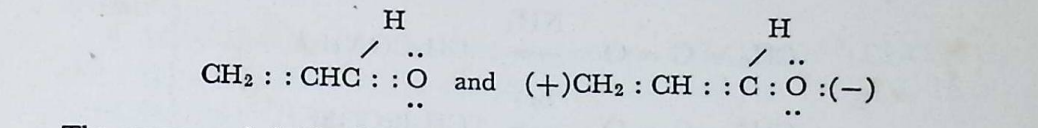
mine is such a reaction, and the formation of the normal oxime proceeds in the same fashion. Thiele's theory of partial valence appears to predict that such 1,2-additions would not occur.

According to current views one would say that a compound containing a conjugated system is in reality a resonance hybrid and has a structure that is intermediate between those of the contributing forms. For acrolein, one would write:



The resonance hybrid will *react* as one of the contributing forms; i.e., either by 1,2-addition to the carbonyl group or the ethylenic linkage, or by 1,4-addition to the conjugated system. Resonance, then, does indicate clearly the possibility of 1,2- and 1,4-addition, but it does not enable us to predict which will take place.

Reduction of Unsaturated Carbonyl Compounds. We have seen that when α,β-unsaturated aldehydes and ketones are reduced, it is the double bond adjacent to the carbonyl group which is reduced first. This occurs during catalytic hydrogenation and even with such reagents as sodium and aluminum amalgam which ordinarily do not affect an ethylenic bond. Probably this is due to a 1,4-addition at the ends of the conjugated system. Because of this fact, the reduction of the carbonyl group in α,β-unsaturated aldehydes and ketones cannot be accomplished by the usual methods. For this type of reaction, aluminum isopropoxide (p. 134) serves admirably; thus acrolein can be converted into allyl alcohol according to the following reaction:

$$CH_2 = CHCHO + 2[H] \xrightarrow{Al[OCH(CH_3)_2]_3} CH_2 = CHCH_2OH$$

KETENES

A group of substances known as the *ketenes* may be considered as a special class of unsaturated ketones. Their structure contains the linkage C = C = O, and they manifest such remarkable reactivity that they are usually considered as a class by themselves. The simplest member of the class is ketene itself formed by passing acetone through a hot tube (p. 166). It can also be prepared by treating bromacetyl bromide with zinc dust. This is a general method of preparing ketenes.

$$CH_2BrCOBr + Zn \longrightarrow CH_2 = C = O + ZnBr_2$$

Ketene is a colorless gas, quite poisonous, with a characteristic, extremely unpleasant odor. It liquefies at $-56°$. Like all the representatives of this class, it is extremely reactive, combining with a great variety of reagents. Some of these addition reactions of ketene

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are illustrated by the following equations:

$$CH_2 = C = O \xrightarrow{H_2O} CH_3COOH$$

$$CH_2 = C = O \xrightarrow{C_2H_5OH} CH_3COOC_2H_5$$

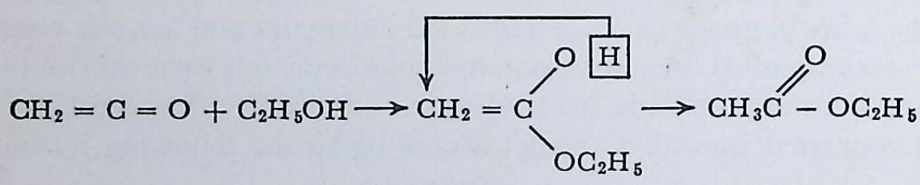
$$CH_2 = C = O \xrightarrow{NH_3} CH_3CONH_2$$

$$CH_2 = C = O \xrightarrow{Br_2} CH_2BrCOBr$$

With the exception of the last reaction it will be noted that the reactions of ketene may be regarded as the addition of a hydrogen atom to the CH_2 group and a residue to the highly unsaturated central carbon atom. Thus, for example:

$$\begin{array}{lll} CH_2 & = C = & O \\ H & & NH_2 \\ H & & OH \end{array}$$

All these processes probably involve a mechanism in which the first reaction involves only the carbonyl group, and is followed by a tautomerization of the enolic compound first formed. This mechanism has been proved in at least one instance. It may be illustrated by the action of alcohol on ketene.



Hypothetical

The ketenes are classified into aldoketenes, having the general formula $RCH = C = O$, and ketoketenes, $R_2C = C = O$. Aldoketenes polymerize to dimolecular compounds so readily that it is very difficult to work with them.

QUESTIONS AND PROBLEMS

1. Give the evidence for the structural formula of allyl alcohol.

2. Compare the reactivity of the following halogen compounds in replacement reactions: (*a*) $CH_3CH_2CH_2CH_2Br$, (*b*) $CH_3CH = CHCH_2Br$, (*c*) $(CH_3)_3CBr$, (*d*) $CH_3CH_2CH = CHBr$, (*e*) $CH_2 = CHCH_2CH_2Br$.

3. What is meant by a conjugated system of double bonds? What type of reaction is peculiar to such a system? Can you account for this special ability of conjugated systems?

4. Write structural formulas for penten-3-oic acid, phorone, 3-methyl-2-pentenal, mesityl oxide, ketene, penten-2-oic acid, vinyl butyrate.

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5. Compare the hydrogen shift in three carbon systems such as vinylacetic acid with that in two-carbon-oxygen systems such as acetoacetic ester.

6. State the rule which describes the addition of halogen acids to α,β-unsaturated acids. What is the mechanism usually suggested for such reactions?

7. Discuss geometric isomerism briefly, considering (*a*) the structural requirements for its occurrence, and (*b*) the ways of determining configuration.

8. Write equations for the reactions between $CH_3CH_2CH = CHCOCH_3$ and $CH_2 = CHCH_2COCH_3$ and the following reagents: CH_3MgI, HCN, NH_2OH, $NaHSO_3$.

9. Outline reactions for the following preparations: (*a*) methyl methacrylate from acetone, (*b*) acrolein from triolein, (*c*) glycerol from propylene, (*d*) methyl acrylate from lactic acid, (*e*) vinylacetic acid from propylene.

10. What is the evidence that both maleic and fumaric acids are ethylene-1,2-dicarboxylic acids and that neither one is $CH_2 = C(COOH)_2$?

11. Write equations for the reactions between methyl ketene and (*a*) water, (*b*) ethyl alcohol, (*c*) ammonia, and (*d*) chlorine.

12. Indicate the reagents and conditions necessary to effect the conversions: (*a*) $(CH_3)_2CHCH = CHCOOH$ to $(CH_3)_2CHCH_2CH_2COOH$, (*b*) $(CH_3)_2C = CHCOCH_3$ to $(CH_3)_2CHCH_2COCH_3$, (*c*) $(CH_3)_2C = CHCOCH_3$ to $(CH_3)_2C = CHCHOHCH_3$, (*d*) fumaric acid to maleic acid.

13. A hydrocarbon with the empirical formula C_6H_{10} was isolated from a reaction mixture. List all the experiments you would propose to perform in order to establish its structure.

14. What products would you expect from the reactions: (*a*) isoprene and maleic anhydride, (*b*) crotonic acid and sodium amalgam in moist ether, (*c*) vinylacetic acid and hydrogen bromide, (*d*) dimethyl ketene and methylmagnesium iodide?

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Chapter 17

DERIVATIVES OF CARBONIC ACID

Carbonic acid, (H_2CO_3), is a dibasic acid which occupies an exceptional position because it does not contain two carboxyl groups. The free acid is not known in the pure state; an aqueous solution of carbon dioxide undoubtedly contains a considerable proportion of carbonic acid in equilibrium with the gas.

$$H_2O + CO_2 \rightleftharpoons O = C(OH)_2$$

The salts of carbonic acid, the carbonates, can be prepared by adding alkali to such aqueous solutions. They are considered fully in books dealing with inorganic chemistry and for this reason need not be further discussed. The derivatives of carbonic acid which are of interest to the organic chemist are usually prepared neither from carbon dioxide nor the carbonates. The acid chloride of carbonic acid, $COCl_2$, known as *phosgene*, is the more usual starting point.

Phosgene. Phosgene is prepared by the action of carbon monoxide and chlorine in the presence of light or a catalyst.

$$CO + Cl_2 \xrightarrow{\text{Light or a catalyst}} C(=O)(Cl)_2$$

Phosgene is also formed by the oxidation of chloroform or carbon tetrachloride. The slow oxidation of chloroform by air has already been mentioned (p. 154).

The two chlorine atoms in phosgene are directly attached to the carbon atom of a carbonyl group. For this reason the reactions of the substance are those of an acid chloride. When treated with water, carbon dioxide and hydrochloric acid are formed.

$$COCl_2 + H_2O \longrightarrow CO_2 + 2HCl$$

With ammonia the diamide is formed. It is known as *urea*.

$$COCl_2 + 2NH_3 \longrightarrow \underset{\text{Urea}}{CO(NH_2)_2} + 2HCl$$

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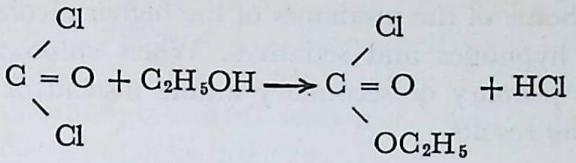
When alcohol and phosgene interact the reaction proceeds in two definite steps; the product of the first step may be isolated before it reacts further. It is known as *ethyl chlorocarbonate.*



Phosgene is a gas at ordinary temperatures (bp 8°). It has a very irritating odor and is extremely poisonous. It was used as a war gas in World War I.

Ethyl Chlorocarbonate. Ethyl chlorocarbonate, $ClCOOC_2H_5$, is prepared from phosgene and ethyl alcohol as just described. It is a liquid insoluble in water, with an unpleasant sharp odor, and boils at 93°. It is also known as *chloroformic ester*, since it may be regarded as the ester of a formic acid in which the hydrogen has been replaced by a chlorine atom. Chloroformic acid itself, ClCOOH, should be the first product fomred by the hydrolysis of phosgene, but it has never been isolated. It probably decomposes at once into hydrochloric acid and carbon dioxide.

Ethyl chlorocarbonate is both an acid chloride and an ester. Many of its reactions are those characteristic of an acyl halide. Hydrolysis, alcoholysis, and ammonolysis all proceed readily.

$$ClCOOC_2H_5 + H_2O \longrightarrow CO_2 + C_2H_5OH + HCl$$

$$ClCOOC_2H_5 + C_2H_5OH \longrightarrow CO(OC_2H_5)_2 + HCl$$

$$ClCOOC_2H_5 + NH_3 \longrightarrow NH_2COOC_2H_5 + HCl$$

The product of the second reaction written above is the diethyl ester of carbonic acid, **ethyl carbonate.** It is the final product of the interaction of phosgene and alcohol. It is a sweet smelling liquid insoluble in water and boiling at 126°. It is easily hydrolyzed and yields carbon dioxide and alcohol.

Urethanes or Esters of Carbamic Acid. The product of the interaction of ammonia and ethyl chlorocarbonate is an ester of carbamic acid, known as a *urethane*, NH_2COOR. **Carbamic acid** itself, NH_2COOH, is unknown in the free state, but its salts are stable compounds. The simplest of these is the ammonium salt which is formed by the direct union of dry carbon dioxide and dry ammonia.

$$2NH_3 + CO_2 \longrightarrow \underset{\text{Ammonium carbamate}}{NH_2COONH_4}$$

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The ethyl ester of carbamic acid (ethyl urethane) is a crystalline solid melting at 50° and boiling at 184°. It has no basic properties. It has a strong hypnotic effect on animals and is often used in physiological experiments. Some of the urethanes of the higher alcohols have been marketed as hypnotics and sedatives. When chlorocarbonic ester reacts with a primary or secondary amine instead of ammonia an **alkyl urethane** results.

$$RNH_2 + ClCOOC_2H_5 \longrightarrow RNHCOOC_2H_5 + HCl$$

Diazomethane. The very interesting and useful substance diazomethane, CH_2N_2, can be prepared from an alkyl urethane. If the urethane obtained from methylamine and chlorocarbonic ester is treated with nitrous acid, the hydrogen on the nitrogen is replaced by a nitroso group; this is similar to the reaction of secondary amines (p. 189). When this nitroso compound is treated with strong alkali, diazomethane is formed.

$$ClCOOC_2H_5 + CH_3NH_2 \longrightarrow CH_3NHCOOC_2H_5 + HCl$$

$$CH_3NHCOOC_2H_5 + HONO \longrightarrow CH_3\underset{\underset{NO}{|}}{N}COOC_2H_5 + H_2O$$

$$CH_3\underset{\underset{NO}{|}}{N}COOC_2H_5 + 2KOH \longrightarrow CH_2N_2 + K_2CO_3 + C_2H_5OH + H_2O$$

Diazomethane is a yellow gas which liquefies at −23° and is very soluble in ether. It reacts with organic acids with the elimination of nitrogen and formation of a methyl ester.

$$CH_2N_2 + RCOOH \longrightarrow RCOOCH_3 + N_2$$

It is often used in ether solution for the preparation of methyl esters. It is slowly decomposed by water, particularly in the presence of mineral acids, forming methyl alcohol and nitrogen. It is an extremely poisonous substance and attacks the skin, lungs, and eyes.

Two formulas for diazomethane are often written, $CH_2\begin{matrix}\diagup N \\ \| \\ \diagdown N\end{matrix}$ and $CH_2 = N \rightleftharpoons N$. The evidence from physical measurements favors the latter.

UREA

Urea, or **carbamide,** $CO(NH_2)_2$, because of its significance in physiological chemistry, is an important derivative of ammonia. It is

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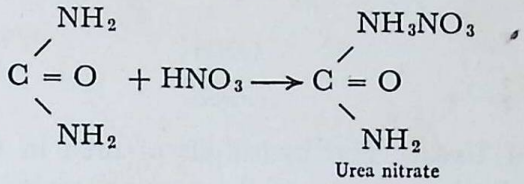
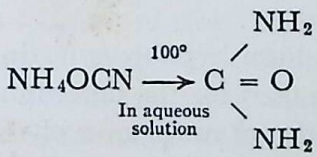
the principal end product of the metabolism of nitrogenous foods in the body and is excreted in the urine.

Urea is the diamide of carbonic acid but, unlike other amides, it has basic properties and forms salts. Both urea and its salts are white crystalline solids soluble in water. Urea itself melts at 132° and decomposes on further heating. In the isolation of urea from urine, the concentrated solution is treated with nitric acid; on cooling, **urea nitrate** crystallizes from the mixture.



Urea is a very weak base (see Fig. 9, p. 188) and its salts are largely hydrolyzed in aqueous solution.

Wöhler's Synthesis of Urea. The first synthesis of urea was accomplished by Wöhler [1] in 1828. He found that, on slow evaporation, a water solution of ammonium cyanate yielded urea.



His discovery awakened great interest. It was the first synthesis of a typical natural product, and did much to break the barrier surrounding the supposedly mysterious chemistry of living things. The preparation of urea from phosgene (p. 326) was accomplished later.

Industrial Preparation of Urea. Urea is now prepared industrially for use as a fertilizer and for the production of certain resins. The reaction employed is similar to one of the general methods of preparing amides, namely, the heating of an ammonium salt. Carbon dioxide and ammonia are heated under pressure. The exact control of the temperature and pressure is important because a series of reversible reactions is involved; a good yield of urea is only obtained under special conditions.

[1] Friedrich Wöhler (1800–1882), professor at the University of Göttingen, Germany.

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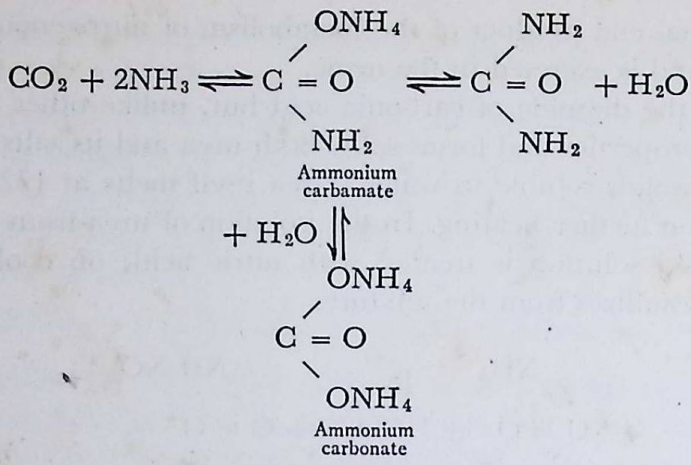

Reactions of Urea. The hydrolysis of urea in water solution is brought about in the presence of the enzyme **urease,** which has been isolated from the soybean. This method forms the basis of a clinical method of determining urea. The amount of ammonia formed from a known weight of sample can be easily determined colorimetrically, or by titration with a standard acid.

$$CO(NH_2)_2 + H_2O \xrightarrow[\text{urease}]{\text{Enzyme}} CO_2 + 2NH_3$$

The reaction with sodium hypobromite (in a sense, the Hofmann reaction) has also been used for the determination of the amount of urea in urine. The volume of nitrogen evolved from a known sample can easily be measured in a suitable apparatus.

$$CO(NH_2)_2 + 3NaOBr + 2NaOH \longrightarrow Na_2CO_3 + N_2 + 3NaBr + 3H_2O$$

As so often happens in organic chemistry, the reaction does not proceed entirely in the way outlined by the above equation. The method must be standardized by finding the amount of nitrogen evolved under certain conditions with known weights of urea.

The Ureides. The hydrogen atoms of urea may be replaced by acyl groups by the action of an acid anhydride on urea. In this way **monoacetyl urea,** $NH_2CONHCOCH_3$, and **diacetyl urea,** $CH_3CONHCONHCOCH_3$, can be prepared. These substances, which may be defined as the acyl derivatives of urea, are known as *ureides.*

$$CO(NH_2)_2 + 2(CH_3CO)_2O \longrightarrow O = C(NHCOCH_3)_2 + 2CH_3COOH$$

The most important ureides are the **cyclic ureides,** derived from

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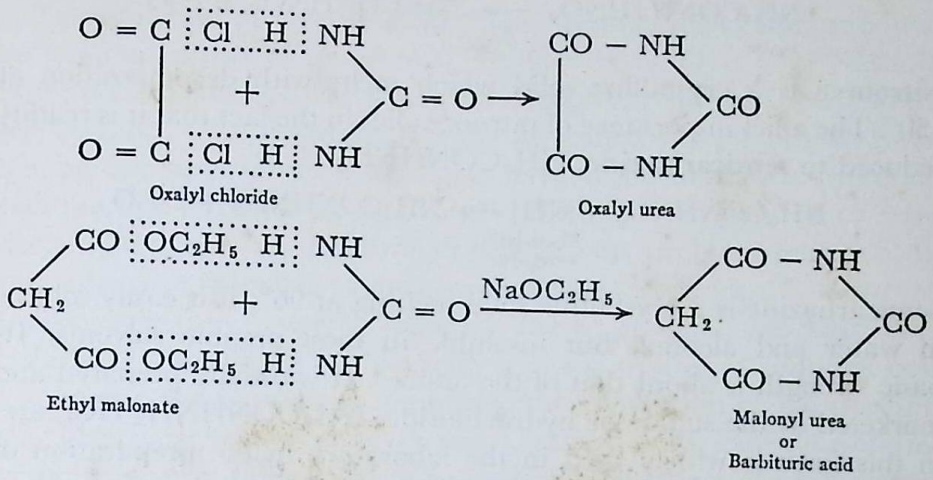
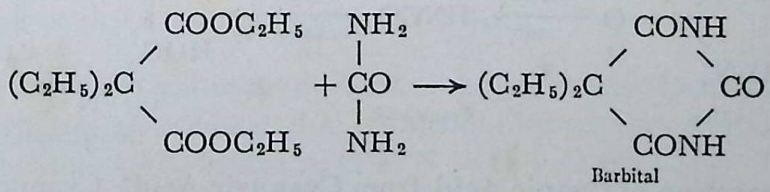
the dibasic acids, oxalic acid and malonic acid. These compounds are conveniently formed by treating urea with the acid chloride or the diethyl ester of the dibasic acid. In the latter reaction sodium ethoxide is used as a catalyst. The second reaction above is reminiscent on the



one hand of the formation of amides from esters (p. 178) and on the other of the condensation of esters with ketones and other esters (p. 272). It is interesting that the formation of cyclic ureides only occurs when a five- or six-membered ring can be formed.

Barbituric Acid. Malonyl urea, the cyclic urea of malonic acid, is also known as *barbituric acid*. It is a weak acid in aqueous solution. We have previously seen that in the cyclic imides (p. 229) a hydrogen on a nitrogen atom between the two carbonyl groups is acidic. This phenomenon is particularly marked in the cyclic ureides. (A further discussion of these cyclic compounds will be reserved for Chap. 31, p. 616).

The ureide of diethylmalonic acid is used in medicine as a soporific, and is known as *barbital* (*veronal*). It is made from the diethyl ester of diethylmalonic acid by a reaction exactly parallel to the one given above.



A variety of barbituric acid derivatives are marketed as soporifics; in these, other alkyl groups replace the ethyl group of barbital.

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Nitrourea and Semicarbazide. One of the hydrogen atoms of urea may be replaced by a nitro group. This is accomplished by adding solid urea nitrate to concentrated sulfuric acid at −3°.

$$NH_2CONH_2{\cdot}HNO_3 \xrightarrow[-3^\circ]{H_2SO_4} NH_2CONHNO_2 + H_2O$$

Nitrourea is a crystalline solid which melts with decomposition at 150°. The chief importance of nitrourea lies in the fact that it is readily reduced to **semicarbazide,** $NH_2CONHNH_2$.

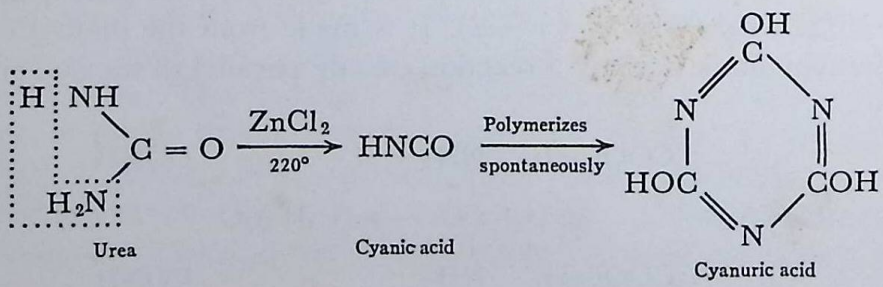
$$NH_2CONHNO_2 + 6[H] \xrightarrow[\text{Electrolytic reduction}]{} NH_2CONHNH_2 + 2H_2O$$

Semicarbazide is a crystalline solid melting at 96°; it is easily soluble in water and alcohol, but insoluble in most organic solvents. Its basic strength is about that of the amines. It is usually prepared and marketed as the sulfate or hydrochloride, $NH_2CONHNH_2{\cdot}HCl$, and in this form is widely used in the laboratory in the preparation of semicarbazones (p. 143).

Alkyl Ureas. Alkyl derivatives of urea in which one or more hydrogen atoms of the urea molecule are replaced by an alkyl group can be made by reactions very similar to those used in the preparation of urea except that an amine is substituted for ammonia. They are similar to urea in their properties and are crystalline solids.

CYANIC ACID

If a molecule of ammonia is eliminated from urea, **cyanic acid,** HNCO, results. This substance polymerizes very easily to **cyanuric acid,** a compound in which three molecules of cyanic acid are joined in a ring. The polymer is the actual substance formed when urea is heated with zinc chloride.



Preparation of Cyanic Acid from Cyanuric Acid. Cyanuric acid is a white solid which is insoluble in almost all solvents. On heating it depolymerizes with the formation of cyanic acid. Cyanic acid is

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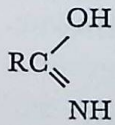
extremely unstable in aqueous solution, decomposing according to the following equation:

$$HNCO + H_2O \longrightarrow CO_2 + NH_3$$

Tautomerism of Cyanic Acid. The formula for cyanic acid may be written in one of two forms, $HOC \equiv N$ or $O = C = NH$; the latter is called the *isocyanic acid formula*. Alkyl derivatives (esters) of the second form, OCNR, are known and are called *alkyl isocyanates*. Esters having the alkyl group attached to oxygen are unknown. Since the two possible formulas for cyanic acid differ by the position of a hydrogen atom and an unsaturated linkage, the problem presented by this substance is similar to the one considered in Chap. 14. However, unlike acetoacetic ester *no tautomeric isomers of cyanic acid* have been isolated. If the liquid cyanic acid or a solution of it contains both tautomeric forms as seems probable, the conversion of the one into the other must be very rapid; so rapid, indeed, as to make the isolation of isomers very difficult if not impossible. This type of tautomerism is more nearly like that of malonic ester (p. 273) than acetoacetic ester. The best information which is available as to the structure of cyanic acid comes from a comparison of the physical properties (particularly the absorption of light) of the acid and the esters (isocyanates RNCO). Since the resemblance is close in many respects the formula OCNH is preferred to HOCN.

The tautomeric behavior of cyanic acid is not unique. On the contrary, there are numerous cases where we are unable to decide definitely on chemical grounds between two tautomeric formulas. Hydrocyanic acid is another example. Its structure might be $HC \equiv N$ like that of a nitrile, or $C \equiv NH$ like that of an isonitrile. Since HCN resembles in physical properties the nitriles rather than the isonitriles, it is believed that the liquid contains chiefly the substance $HC \equiv N$. The amides might be written



instead of $RCONH_2$. Here, also, indirect evidence leads us to prefer one of the two tautomeric formulas, namely $RCONH_2$.

Reactions of Cyanic Acid. One of the tautomeric forms of cyanic acid contains an accumulation of double linkages on a carbon atom similar to that found in ketene: $H - N = C = O$ and $CH_2 = C = O$. It is not surprising, therefore, that cyanic acid is very reactive and that its reactions resemble those of ketene. It reacts with water to form ammonia and carbon dioxide, with alcohols to form urethanes,

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with ammonia to form urea, and with a primary or secondary amine to form a substituted urea.

$$O = C = NH + H_2O \longrightarrow \underset{\text{Carbamic acid}}{HOC(=O) - NH_2} \longrightarrow CO_2 + NH_3$$

$$O = C = NH + C_2H_5OH \longrightarrow \underset{\text{Urethane}}{C_2H_5OC(=O) - NH_2}$$

$$O = C = NH + NH_3 \longrightarrow NH_2CONH_2$$

$$O = C = NH + RNH_2 \longrightarrow RNHC(=O) - NH_2$$

Urea itself may sometimes be used as a source of nascent cyanic acid, since urea on losing a molecule of ammonia passes into cyanic acid. Thus, if urea is heated with normal butyl alcohol for some hours, the small amount of cyanic acid which is slowly formed reacts with the butyl alcohol and forms a urethane.

$$NH_2CONH_2 \xrightarrow{\text{Slowly}} NH_3 + HNCO$$

$$HNCO + C_4H_9OH \longrightarrow \underset{\substack{\text{Butylcarbamate}\\ \text{(a urethane)}}}{NH_2COOC_4H_9}$$

This is a convenient method of preparing certain urethanes.

Esters of Cyanic Acid — The Alkyl Isocyanates. It has already been pointed out that alkyl derivatives (esters) of the structure RNCO are known and are called *alkyl isocyanates*, while esters of the structure ROCN are unknown. The alkyl isocyanates are prepared by the action of an alkyl iodide on potassium or, better, silver cyanate.

$$AgNCO + RI \longrightarrow RN = C = O + AgI$$

Another method of preparing alkyl isocyanates is by the oxidation of an isonitrile.

$$RNC + HgO \longrightarrow RNCO + Hg$$

The alkyl isocyanates are volatile liquids with a very disagreeable odor. They are somewhat unstable, tending to polymerize to trimers (esters of isocyanuric acid). The isocyanates are hydrolyzed by warming with alkali with the formation of a primary amine and carbon

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dioxide. This fact proves that the alkyl group is attached to nitrogen.

$$CH_3N = C = O + H_2O \xrightarrow{NaOH} CH_3NH_2 + CO_2$$

The isocyanates combine with alcohol to form alkyl urethanes and with amines to form disubstituted ureas.

$$RNCO + R'OH \longrightarrow RNHCOOR'$$

$$RNCO + R'NH_2 \longrightarrow RNHCONHR'$$

A few of the isocyanates (in which R is a large group) are used to identify alcohols and amines, since the urethanes and the disubstituted ureas obtained are crystalline solids which have definite melting points.

Isocyanates from Acid Azides. An important reaction for the preparation of isocyanates (or their addition products) from acids involves compounds known as *acid azides*, acyl derivatives of hydrazoic acid, HN_3. These compounds may be prepared by the interaction of acid chlorides and sodium azide.

$$RCOCl + NaN_3 \longrightarrow \underset{\text{An acid azide}}{RCON_3} + NaCl$$

The acid azides are unstable and reactive compounds. On heating they lose nitrogen gas and undergo a **molecular rearrangement,** known as the **Curtius rearrangement.**

$$RCON_3 \longrightarrow N_2 + \left[RCON\begin{matrix}/\\\backslash\end{matrix}\right] \longrightarrow \underset{\text{Isocyanate}}{RN = C = O}$$

The compound $RCON\begin{matrix}/\\\backslash\end{matrix}$, which is probably the first product, contains a monovalent nitrogen atom and has therefore only a momentary existence. By the shift of the alkyl group, all the atoms can assume their normal valency.

The importance of the Curtius reaction lies in the fact that the resulting isocyanate can be transformed by the reactions given above into a primary amine, a urethane, or a urea derivative. Thus, by the use of the azides, the same type of degradation may be accomplished as by the Hofmann reaction.

$$RCH_2COOH \longrightarrow RCH_2COCl \longrightarrow RCH_2CON_3 \longrightarrow RCH_2NCO \longrightarrow RCH_2NH_2$$

The acid azides may also be formed by the action of nitrous acid on the acyl derivatives of **hydrazine,** NH_2NH_2. These compounds in turn may be prepared by the action of hydrazine on esters or amides.

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$$RCOOC_2H_5 + NH_2NH_2 \longrightarrow RCONHNH_2 + C_2H_5OH$$

$$RCONHNH_2 + HNO_2 \longrightarrow RCON_3 + 2H_2O$$
$$(NaNO_2 + HCl)$$

Fulminic Acid. A very unstable compound isomeric with cyanic acid is fulminic acid, for which the formula, CNOH, must be written. The electronic formula is probably $H : \ddot{O} : N :: C :$ or $HON \equiv C$. It should be noted that, although this substance is an isomer of cyanic acid, it is not a tautomeric form since it cannot pass into cyanic acid by a mere transfer of hydrogen. It differs from cyanic acid in the order in which the carbon, nitrogen, and oxygen atoms are arranged. The mercury salt of this acid has been known for a long time because it is formed when mercuric nitrate, alcohol, and nitric acid are brought together. It is a powder, insoluble in alcohol and water. When dry it is a sensitive explosive, detonating on a slight blow. It is known as **mercury fulminate** and is used extensively in the manufacture of priming caps which explode when struck a sharp blow. A similar compound is **silver fulminate,** prepared in the same way from silver nitrate, nitric acid, and alcohol. The free fulminic acid can be prepared from its salts. It is a very unstable, volatile compound which is extremely poisonous.

OTHER AMMONIA DERIVATIVES OF CARBONIC ACID

If we imagine that all the hydroxyl groups of the hypothetical ortho carbonic acid, $C(OH)_4$, are replaced by NH_2 groups, the compound $C(NH_2)_4$ would result. This substance is unknown, but the compound which would result from it by loss of a molecule of ammonia is a well-known and an important substance. It is **guanidine,** $C(=NH)(NH_2)_2$. By further loss of ammonia, guanidine passes into another interesting substance, **cyanamide,** NH_2CN. We thus have a series of compounds each formed from the other by loss of ammonia. This series is analogous to that formed from the dehydration products of **ortho carbonic acid.**

RELATIONSHIP OF DERIVATIVES OF CARBONIC ACID

Hypothetical Ortho Form (Unknown)	*Loss of H_2O or NH_3*		*Loss of H_2O or NH_3*	
$(HO)_2C(OH)_2$	$\xrightarrow{-H_2O}$	$O = C(OH)_2$ Carbonic acid	$\underset{+H_2O}{\overset{-H_2O}{\rightleftharpoons}}$	$O = C = O$
$(HO)_2C(NH_2)_2$	$\xrightarrow{-H_2O}$	$O = C(NH_2)_2$ Urea	$\underset{+NH_3}{\overset{-NH_3}{\rightleftharpoons}}$	$O = C = NH$ or $HOC \equiv N$ Cyanic acid (polymer cyanuric acid $(HNCO)_3$)

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$$(H_2N)_2C(NH_2)_2 \xrightarrow{-NH_3} \underset{\text{Guanidine}}{HN = C(NH_2)_2} \underset{+NH_3}{\overset{-NH_3}{\rightleftharpoons}} \underset{\text{Cyanamide}}{HN = C = NH \text{ or } H_2NC \equiv N}$$

Guanidine. We have just seen that guanidine is related to the ortho form of carbonic acid. Therefore, it is not surprising that it may be prepared by the action of ammonia on the ethyl ester of ortho carbonic acid.

$$\underset{\text{Ethyl ortho carbonate}}{C(OC_2H_5)_4} + 3NH_3 \xrightarrow{160^\circ} C\begin{matrix} NH_2 \\ \\ NH_2 \end{matrix} = NH + 4C_2H_5OH$$

This tetraethyl ester of the unknown ortho form of carbonic acid may be prepared by the action of potassium ethoxide on carbon tetrabromide. (This reaction is exactly analogous to the method of preparation of the esters of orthoformic acid [p. 101].)

Other more convenient methods of preparing guanidine are available. It can be prepared by the addition of ammonia to cyanamide.

$$NH_2CN + NH_3 \longrightarrow (NH_2)_2C = NH$$

Guanidine is a colorless, very hygroscopic, crystalline solid which is exceedingly soluble in water. Surprisingly enough it is as strong a base as sodium hydroxide (see Fig. 9). It is usually prepared and used in the form of one of its salts. For example, in the preparation of guanidine from cyanamide the source of the ammonia is ammonium chloride, and the hydrochloride of guanidine is the actual product.

$$CNNH_2 + NH_4Cl \longrightarrow HN = C(NH_2)_2 \cdot HCl$$

Reactions of Guanidine. Guanidine is readily hydrolyzed with the formation of urea and ammonia. The reaction is catalyzed by the presence of bases.

$$(NH_2)_2C = NH + H_2O \xrightarrow{\text{Alkali}} CO(NH_2)_2 + NH_3$$

When guanidine carbonate is fused with potassium hydroxide a molecule of ammonia is lost and **cyanamide** is formed.

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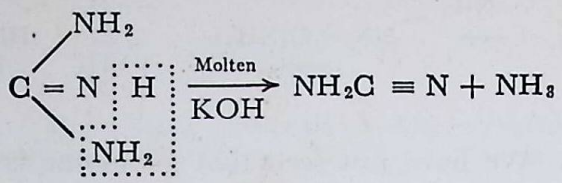
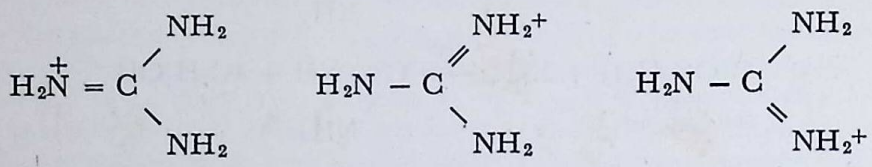


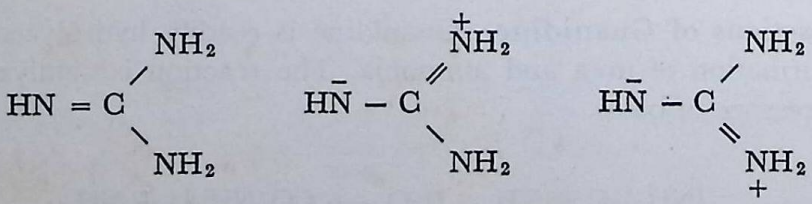
Structure of Guanidinium Ion. The salts of guanidine such as guanidinium chloride, $(NH_2)_2CNH_2Cl$, contain the ion $[(NH_2)_2CNH_2]^+$. For such an ion, three formulas might be written:



These formulas clearly meet the requirements for resonance. And, since the three structures are equivalent, the resonance energy will be large and the formation of the guanidinium ion will be stabilized. Consistent with this is the fact that guanidine is a strong base, approximately 10,000 times stronger than the simple aliphatic amines.

The shortening of linkages that accompanies resonance is shown very clearly in the guanidinium salts. The normal distance between centers in the C—N bond is 1.48Å and in the C=N linkage is 1.28Å. The X-ray analysis of the guanidinium ion in the solid salts shows a perfectly symmetrical arrangement of three NH_2 groups about a central carbon atom with a distance between the carbon and nitrogen atoms of only 1.18Å. The symmetry of the ion, which excludes any formula in which one nitrogen atom is bound differently from the other two, is particularly to be noted.

Guanidine itself (the free base) also exhibits resonance but the resonance energy is much less than with the ion. Therefore, salt formation is favored by resonance. The *relatively* weak resonance of the free base involves three structures. Unlike the resonating structures of the *guanidinium ion* these structures are not equivalent, the first being more important than the others.



The shift from the first formula on the left to the second involves the following electronic change, which is like that encountered in the undissociated fatty acids (p. 81).

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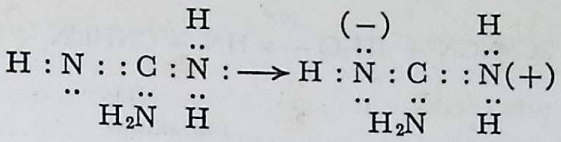

Cyanamide. Cyanamide, $NH_2C \equiv N$, may be regarded as the nitrile of carbamic acid, NH_2COOH. As in cyanic acid and many other compounds, the position of the hydrogen atom in cyanamide cannot be considered as definitely established. Many of the reactions of the substance correspond to the formula $NH = C = NH$, rather than $NH_2C \equiv N$, and the liquid may be a mixture of both forms. Cyanamide may be prepared from guanidine by the method given in a preceding paragraph. It is also formed from urea by the action of dehydrating agents and by the interaction of ammonia and cyanogen chloride.

$$CO(NH_2)_2 \xrightarrow{SOCl_2} CNNH_2 + H_2O$$

$$ClCN + NH_3 \longrightarrow NH_2CN + HCl$$

Cyanamide is a deliquescent, colorless solid melting at 41° to 42°. It is soluble in water, alcohol, and ether. It has very weakly basic properties; even its salts with strong acids are completely hydrolyzed by water. It is also a weak acid, and forms sodium and potassium salts which are stable in aqueous solution. Free cyanamide is difficult to keep in a pure state as it passes over into dicyandiamide in the presence of moisture. On hydrolysis cyanamide yields urea.

$$CNNH_2 + H_2O \longrightarrow CO(NH_2)_2$$

Calcium Cyanamide. This material, prepared by heating calcium carbide and nitrogen in an electric furnace, is a substance of great commercial importance.

$$CaC_2 + N_2 \longrightarrow CaNCN + C$$

Crude calcium cyanamide, often called *lime-nitrogen*, is used as a fertilizer. In the soil it undergoes hydrolysis to cyanamide which, in turn, is hydrolyzed to urea, and finally to ammonia.

In addition to its use as a fertilizer, calcium cyanamide also serves as the starting material for the synthesis of a number of the substances which we have considered in this chapter. For example, guanidine can be prepared from calcium cyanamide, through the intermediate formation of dicyandiamide.

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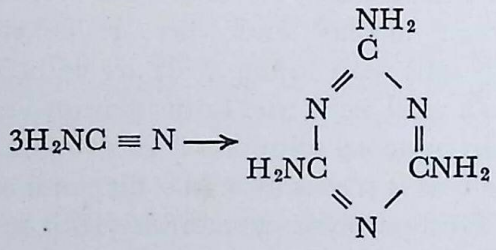
$$2CaNCN + 4H_2O \xrightarrow{100^\circ} HN = \underset{\underset{NH_2}{|}}{C}NHCN + 2Ca(OH)_2$$

Dicyandiamide

$$HN = \underset{\underset{NH_2}{|}}{C}NHCN + 2NH_4NO_3 \xrightarrow{\text{Melted}} 2NH_2C\begin{matrix} NH \\ // \\ \\ \backslash \\ NH_2 \cdot HNO_3 \end{matrix}$$

Dicyandiamide is a colorless crystalline compound, melting at 205°, rather soluble in alcohol and water. It has no pronounced acid or basic properties. On reduction it yields guanidine and methylamine.

Melamine. When cyanamide or dicyandiamide is heated under conditions such that hydrolysis cannot take place, a trimer of cyanamide is formed. The usual practice is to heat dicyandiamide with liquid ammonia under pressure as a solvent. The dicyandiamide probably dissociates in part to form cyanamide, which can react with more dicyandiamide to furnish the trimer. The synthesis may be written as a reaction of the monomer.



Melamine, which is the ammonia analogue of cyanuric acid, has important industrial applications since, on condensation with formaldehyde, it forms useful products of high molecular weight (p. 515).

QUESTIONS AND PROBLEMS

1. Write structural formulas for barbituric acid, diazomethane, semicarbazide, dicyandiamide, melamine, ethyl urethane, and guanidine.

2. Outline the steps involved in each of the following transformations: (*a*) $CH_3NHCOOC_2H_5$ to CH_2N_2, (*b*) CH_3CH_2COOH to $CH_3CH_2NH_2$, (*c*) CH_3CH_2COOH to $CH_3CH_2NHCOOCH_3$, (*d*) $NH_2CONH_2 + C_4H_9OH$ to $NH_2COOC_4H_9$.

3. Show the equilibria involved in the preparation of urea from carbon dioxide and ammonia.

4. Compare the equilibria shown by cyanic acid, acetoacetic ester, and vinylacetic acid.

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5. Write balanced equations for the reactions between urea and (*a*) sodium hypobromite, (*b*) acetic anhydride, and (*c*) malonic ester.

6. Prepare a chart showing the preparation of calcium cyanamide and its conversion to dicyandiamide, guanidine, and melamine.

7. Outline the reactions involved in the preparation of semicarbazide from urea. Show by equations the use of semicarbazide as an organic reagent.

8. Compare by means of equations the reactions of cyanic acid and of ketene.

9. Write formulas for the resonance forms of guanidine. What is the evidence for resonance in the guanidinium ion?

10. Give two methods of preparing methyl isocyanate. Write the reaction between methyl isocyanate and dilute aqueous alkali.

11. An aqueous solution contains sodium chloride and either ammonium acetate, acetamide, or urea. What tests would you use to determine which of the three latter named substances was present?

12. Arrange the following compounds in the order of increasing basicity: $CH_3CH_2CONH_2$, $CH_3NHCOOC_2H_5$, $(CH_3)_2C{=}NH$, $(CH_3NH)_2C{=}NCH_3$, $CH_3C\begin{matrix}\diagup NH_2\\ \diagdown\!\!\!\!\diagdown NH\end{matrix}$.

13. Indicate the steps in the synthesis of (*a*) $CH_3CH_2CON_3$, (*b*) $CH_3-\underset{\underset{H}{|}}{C}\begin{matrix}\diagup CO-NH\diagdown\\ \diagdown CO-\underset{\underset{CH_3}{|}}{N}\diagup\end{matrix}CO$, (*c*) $(CH_3)_2NCONHCH_3$, (*d*) $CO(NHCOCH_3)_2$.

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Chapter 18

COMPOUNDS CONTAINING SULFUR

In many of the preceding chapters, we have been concerned with substances which may be regarded as derivatives of water, ammonia, or carbonic acid. We shall now consider some organic compounds which are derivatives of hydrogen sulfide or related to carbon disulfide (CS_2). Since sulfur occurs immediately under oxygen in the same group of the periodic table, there is a marked similarity between sulfur and oxygen compounds. Perhaps the greatest difference between the two elements lies in the fact that in many substances sulfur has a valence greater than two. Thus, we shall find large classes of organic sulfur compounds in which the element has a higher valence and for which no analogy exists in the compounds containing oxygen. However, the organic sulfur compounds in which the valence of sulfur is two, closely parallel the corresponding oxygen compounds. Because of this close analogy much of the chemistry of simple sulfur compounds may be easily related to information already acquired.

DERIVATIVES OF HYDROGEN SULFIDE

The monoalkyl derivatives of hydrogen sulfide, RSH, are known as *mercaptans* or *thiols;* they are the sulfur analogs of the alcohols. The sulfur analogs of the ethers are the dialkyl derivatives of hydrogen sulfide, RSR; they are known as the alkyl sulfides or thioethers.

Mercaptans. The commonest method of preparing the mercaptans is by the interaction of an alkyl halide and the monopotassium salt of hydrogen sulfide in alcoholic solution. This reaction is analogous to the preparation of an alcohol by the hydrolysis of an alkyl halide.

$$C_2H_5Br + KSH \longrightarrow C_2H_5SH + KBr$$

Since an alkyl halide is prepared from an alcohol, we have here an indirect method of replacing an hydroxyl group by a **sulfhydryl group** (SH). A direct method of accomplishing the interchange of these groups consists in passing the vapors of an alcohol mixed with hydrogen sulfide over certain catalysts at an elevated temperature.

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$$ROH + H_2S \xrightarrow[350^\circ]{ThO_2} RSH + H_2O$$

Properties of the Mercaptans. The boiling points of the simpler mercaptans are given in the table. **Ethyl mercaptan** is a colorless liquid with an intensely disagreeable odor. It can be detected by its odor in extraordinarily small amounts. Even the lower members of the series are but slightly soluble in water. They dissolve in sodium hydroxide solution, however, with the formation of a sodium salt which is appreciably hydrolyzed. The mercaptans are thus somewhat more acidic than the corresponding alcohols.

PHYSICAL PROPERTIES OF THE SIMPLER MERCAPTANS

Name	*Formula*	*Boiling Point*
Methyl mercaptan	CH_3SH	6°
Ethyl mercaptan	C_2H_5SH	37°
n-Propyl mercaptan	C_3H_7SH	68°
Isopropyl mercaptan	$(CH_3)_2CHSH$	59°

The 1,2-dithiol derived from glycerin is known as *BAL*. It forms metallic derivatives with many of the heavy metals and is therefore valuable in the treatment of poisoning by heavy metals.

$$\begin{array}{l} CH_2CHCH_2OH \\ \;\;|\;\;\;\;|\;\;\;\;

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$$RCO\,\boxed{OH + H}\,SC_2H_5; \quad RCO\,\boxed{OH + H}\,OC_2H_5$$

The direct proof of the origin of water during esterification has been considered on page 96.

Sulfonic Acids. In their behavior toward oxidizing agents, mercaptans are entirely different from alcohols. The action of a powerful oxidizing agent adds oxygen and increases the valence of the sulfur instead of removing hydrogen. The final product of such an oxidation is a substance known as a *sulfonic acid.*

$$C_2H_5SH + 3[O] \longrightarrow \underset{\text{Ethane sulfonic acid}}{C_2H_5SO_2OH}$$

The sulfonic acids may be regarded as derivatives of sulfuric acid in which one hydroxyl has been replaced by an alkyl group. They differ greatly from the esters of sulfuric acid (e.g., $C_2H_5OSO_3H$), which are the result of the replacement of a hydrogen atom in sulfuric acid by an alkyl group. Unlike the esters of sulfuric acid, the sulfonic acids are not hydrolyzed by boiling with alkali. The sulfonic acids are strong acids comparable with the mineral acids. They are crystalline solids, easily soluble in water.

The Alkyl Sulfides. The sulfur analogs of the ethers are the alkyl sulfides or **thioethers.** The methods of preparation are illustrated by the following equations. The first can be used for the preparation of mixed sulfides, the second only for the synthesis of symmetrical compounds.

$$C_2H_5SNa + CH_3I \longrightarrow C_2H_5SCH_3 + NaI$$
$$2C_2H_5I + K_2S \longrightarrow (C_2H_5)_2S + 2KI$$

The simple alkyl sulfides boil lower than the mercaptans of the same carbon content. The alkyl sulfides have a disagreeable odor, though not so penetrating as that of the mercaptans. **Allyl sulfide,** $(CH_2 = CHCH_2)_2S$, is the chief constituent of oil of garlic. They are all insoluble in water and soluble in organic solvents. They show no acidic properties but form addition compounds with a number of metallic salts. These addition compounds are usually insoluble in water. An example of such a compound is the addition product of ethyl sulfide with mercuric chloride, $(C_2H_5)_2S{\cdot}HgCl_2$.

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Mustard Gas. During World War I a dihalogen derivative of an alkyl sulfide was used extensively as a poisonous gas. This is the compound known as *β,β′-dichloroethyl sulfide.*

$$ClCH_2CH_2SCH_2CH_2Cl$$

It is a liquid which boils at 215°. It is insoluble in water but penetrates the skin when in contact with it, and in a few hours produces a very painful burn and blister. Because of this action it was an extremely potent war gas. The exposure of a considerable portion of the body to the fumes of this liquid for a short time will produce a burn sufficient to cause serious injury and often death. The compound can be prepared by the direct interaction of ethylene and sulfur chloride.

$$2C_2H_4 + S_2Cl_2 \longrightarrow (CH_2ClCH_2)_2S + S$$

A more orthodox method of preparing this sulfide is indicated by the following series of reactions which starts with ethylene.

$$C_2H_4 \xrightarrow{HOCl} ClCH_2CH_2OH \xrightarrow{Na_2S} S(CH_2CH_2OH)_2 \xrightarrow{HCl} S(CH_2CH_2Cl)_2$$

Disulfides. Cautious oxidation of the mercaptans may result in the formation of a disulfide, RSSR, instead of a sulfonic acid. For example, slow oxidation by the air of ethyl mercaptan, or the action of iodine on an alkaline solution, produces diethyl disulfide.

$$2C_2H_5SH \xrightarrow[\text{Air}]{[O]} C_2H_5S - SC_2H_5 + H_2O$$

$$2C_2H_5SNa + I_2 \longrightarrow C_2H_5S - SC_2H_5 + 2NaI$$

Another method of preparing disulfides is to heat an alkyl halide with potassium disulfide.

$$2C_2H_5Br + K_2S_2 \longrightarrow C_2H_5S - SC_2H_5 + 2KBr$$

When 1,2-dichloroethane and sodium polysulfide react the product is thiokol, $(C_4H_8S_4)_x$, one of the synthetic rubbers mentioned earlier (p. 118).

Sulfonium Salts. Alkyl sulfides combine with one molecule of an alkyl halide to form a trialkyl sulfonium salt. These compounds are crystalline solids which are soluble in water.

$$(C_2H_5)_2S + C_2H_5I \longrightarrow \underset{\text{Triethylsulfonium Iodide}}{(C_2H_5)_3SI}$$

The corresponding base may be prepared by the action of silver hydroxide.

$$(C_2H_5)_3SI + AgOH \longrightarrow (C_2H_5)_3SOH + AgI$$

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The sulfonium bases are strong bases comparable to the quaternary ammonium hydroxides. They may be obtained as deliquescent crystalline solids. A brief discussion of these compounds in an earlier chapter (p. 195) emphasized that the essential reaction is the formation of the ion R_3S^+. The salts are thus aggregates of the ions R_3S^+ and X^-, and the corresponding hydroxides are composed of the ions R_3S^+ and OH^-.

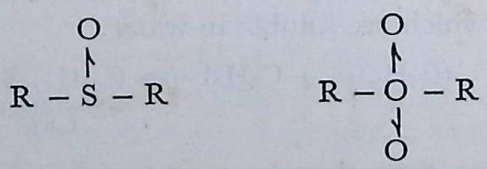
Sulfoxides and Sulfones. Oxidation of the alkyl sulfides with such reagents as hydrogen peroxide or nitric acid causes the addition of one or two atoms of oxygen without disruption of the molecule. The first product is called a *sulfoxide* and has the general formula R_2SO; the final product is a **sulfone,** R_2SO_2.

$$(C_2H_5)_2S + \underset{(H_2O_2)}{[O]} \longrightarrow \underset{\text{Diethyl sulfoxide}}{(C_2H_5)_2SO} \xrightarrow[(HNO_3)]{[O]} \underset{\text{Diethyl sulfone}}{(C_2H_5)_2SO_2}$$

The sulfoxides and sulfones are usually crystalline solids. Dimethyl sulfone melts at 109°; the liquid boils at 238°.

The Structure of Sulfoxides and Sulfones. Inspection of the electronic formula of an alkyl sulfide shows that the sulfur atom has four unshared electrons. Combination between oxygen and this sulfur atom can take place with the formation of coordinate covalences; in this way the oxygen and sulfur atoms have octets.

The process parallels the formation of amine oxides from tertiary amines. Here, as in amine oxides, we usually represent the coordinate covalence by a singly barbed arrow pointing toward the acceptor atom.



Very frequently, completely noncommittal formulas, such as R_2SO and R_2SO_2, are used for sulfoxides and sulfones.

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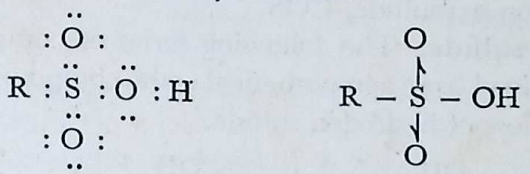
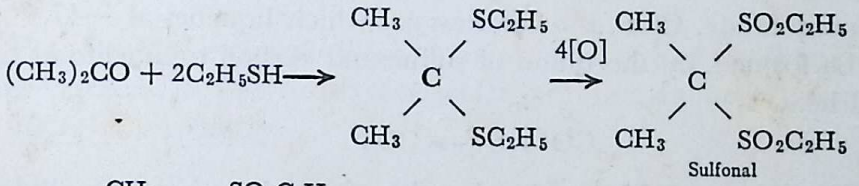
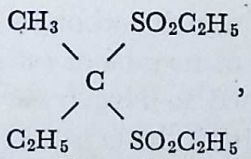
Formerly the sulfoxides were written with double bonds between oxygen and sulfur, just as the amine oxides were formerly written with a pentacovalent nitrogen atom. Structures such as these, $R-\underset{\underset{O}{\|}}{S}-R$ and $R_2S\begin{matrix}\diagup\!\!\!\diagup O\\ \diagdown\!\!\!\diagdown O\end{matrix}$, in which the sulfur atom has ten and twelve electrons respectively in its outer shell, are no longer used.

In the sulfonic acids two of the oxygen atoms are linked to sulfur by coordinate covalences. The electronic and condensed structural formulas for a sulfonic acid are, therefore:

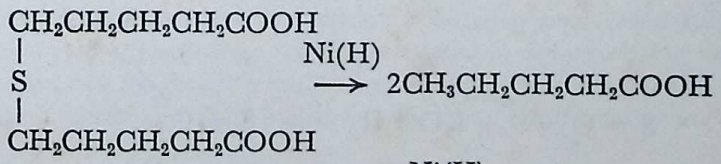


Disulfones as Drugs. Two sulfur compounds which are prepared for use as soporifics are **sulfonal** and **trional.** Both of these are colorless solids, slightly soluble in water. They are prepared by first forming the sulfur analog of an acetal from a ketone and a mercaptan, and then oxidizing the product to the corresponding sulfone. The method is illustrated by the synthesis of sulfonal.



Trional,  , is made in exactly the same way except that ethyl methyl ketone is used instead of acetone.

Removal of Sulfur from the Sulfur Compounds. The organic sulfides and disulfides are converted to sulfur-free products when they are heated in an organic solvent with a nickel catalyst (Raney nickel). The hydrogen used in the reaction is hydrogen retained by the catalyst in its preparation.



$$RSSR \xrightarrow{Ni(H)} 2RH$$

Sulfoxides and sulfones undergo a similar reaction, oxygen as well as sulfur being removed.

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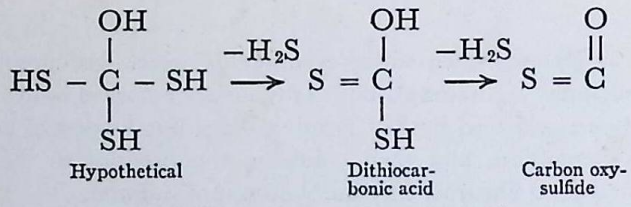
DERIVATIVES OF THE SULFUR ANALOGS OF CARBONIC ACID

In the last chapter a variety of compounds were discussed which were derived from the ortho form of carbonic acid by the replacement of one or more hydroxyl groups by NH_2 groups (p. 336). If we similarly imagine that the hydroxyl group of orthocarbonic acid is replaced by the SH group, various types of interesting compounds result.

Some of these may be regarded as derived from the ortho form of carbon disulfide, the sulfur analog of carbon dioxide, while others are related to carbon oxysulfide, COS.

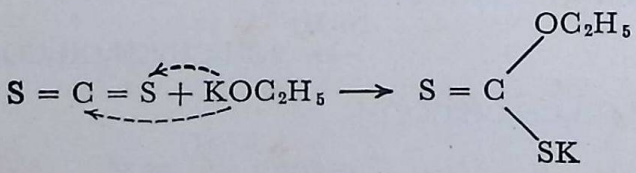
Carbon Oxysulfide. The following series of compounds may be regarded as derived from a hypothetical ortho compound, $HOC(SH)_3$, by progressive loss of hydrogen sulfide.



Carbon oxysulfide, COS, is a colorless gas which liquefies at −47.5°. It can be formed by the union of sulfur and carbon monoxide at a low red heat.

$$CO + S \longrightarrow COS$$

The Xanthates. Dithiocarbonic acid, of which carbon oxysulfide is the anhydride, is known only in the form of its salts or esters. The acid esters which have an alkyl group attached to oxygen are known as the *xanthic acids* or *xanthogenic acids*. They have the general formula $ROC(=S)-SH$; the corresponding salts, $ROC(=S)-SNa$, are known as the *xanthates*. They are formed by the addition of an alkoxide to carbon disulfide.



The same reaction proceeds if an alcohol, potassium hydroxide, and carbon disulfide are mixed. A very important xanthate is that formed

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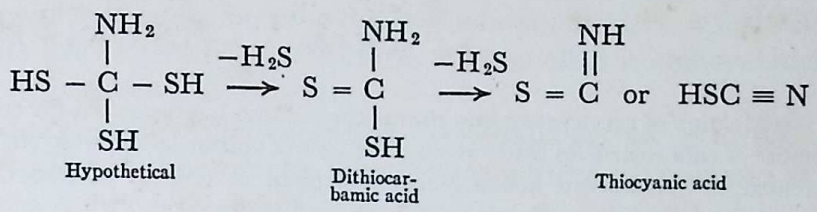
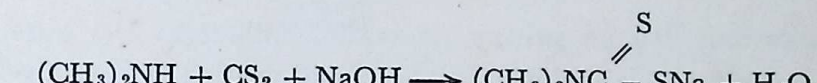
from cellulose; this has been referred to in connection with the manufacture of artificial silks.

Dithiocarbamic Acids. The following series of substances containing sulfur and nitrogen may be regarded as derived from the ortho compound $NH_2C(SH)_3$.



This series is analogous to the one which includes carbamic acid and cyanamide (Chap. 17).

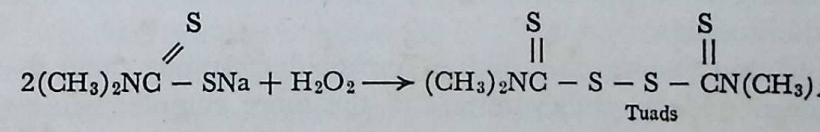
Dithiocarbamic acid is unknown in the free state, but the salts of its alkyl derivatives are readily formed if carbon disulfide and alkali are allowed to act on an amine.



The salts of the dialkyl-dithiocarbamic acids are of importance in the preparation of two substances which are used in large quantities in the rubber industry.

Accelerators of Vulcanization of Rubber. A number of organic sulfur compounds are used in large quantities in the rubber industry to accelerate the process of vulcanization (p. 113). Twenty-five years ago it was discovered that certain organic nitrogen compounds greatly decreased the time required for vulcanizing rubber. One of the compounds first used was thiocarbanilide (p. 351). It is now known that at least ten different classes of organic compounds will accelerate the vulcanization process. All the acceierators contain either sulfur or nitrogen or both elements. Among the sulfur-free accelerators may be mentioned hexamethylenetetramine (p. 150), aliphatic amines, derivatives of guanidine containing the phenyl group, C_6H_5- (p. 417), and condensation products of aldehydes and amines.

Two sulfur compounds which are capable of bringing about rapid vulcanization at a particularly low temperature are closely related to dithiocarbamic acid. *Tuads* is the trade name of the disulfide formed by oxidizing the dithiocarbamic acid prepared from dimethylamine. (The interaction of carbon disulfide and dimethylamine was considered above.)



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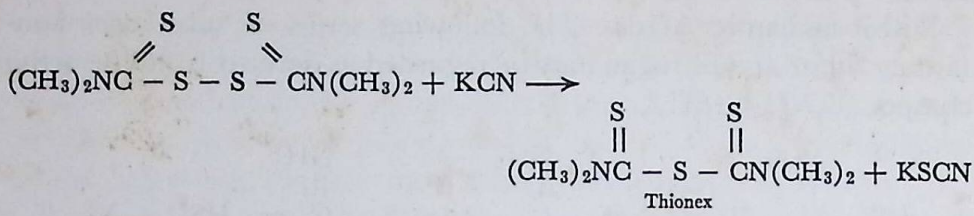
When the product known as *Tuads* is treated with potassium cyanide, an atom of sulfur is removed. The monosulfide which is formed is sold under the name of *Thionex*.



The introduction of accelerators into the rubber industry has decreased the cost of manufacture of rubber articles by decreasing the time of vulcanization, which in turn has decreased the investment in machinery and plant. A finished product of far superior and more uniform quality has also been produced.

Thiocyanic Acid and the Thiocyanates. Thiocyanic acid, HSCN, is the sulfur analog of cyanic acid. It is prepared from its salts, which are readily formed by heating cyanides with sulfur.

$$KCN + S \longrightarrow \underset{\text{Potassium thiocyanate}}{KSCN}$$

Thiocyanic acid is a white crystalline solid melting at 5° to a yellow liquid which soon polymerizes. The acid is readily soluble in water. The potassium, sodium, and ammonium salts are soluble; a number of those with the heavy metals are insoluble. The ferric salt, $Fe(CNS)_3$, is formed on bringing together a soluble ferric salt and a soluble thiocyanate. Its characteristic red color serves as a very sensitive test for ferric ions. The insoluble mercuric salt, $Hg(SCN)_2$, burns when ignited forming a very long voluminous ash. This striking phenomenon has been called the formation of *Pharaoh's serpents*.

Unlike cyanic acid, the alkyl derivatives of both the tautomeric forms of thiocyanic acid have been prepared. They are the so-called **normal esters,** $R - S - C \equiv N$, and the **isoesters,** $S = C = NR$. Thiocyanic acid itself is a strong acid in dilute aqueous solution and probably has the structure $HSC \equiv N$, although it may be a mixture of the two tautomeric forms. The normal esters are prepared by the action of an alkyl halide on potassium thiocyanate.

$$KSCN + CH_3I \longrightarrow CH_3SC \equiv N + KI$$

On heating to a high temperature the normal esters rearrange to form the isoesters.

Many thiocyanates are used as insecticides. Among them may be mentioned dodecyl thiocyanate and the more complex ether-ester,

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$C_4H_9OCH_2CH_2OCH_2CH_2SCN$, one of a group of complex thiocyanates used under the general name of *Lethanes*.

Alkyl Isothiocyanates or Mustard Oils. The isothiocyanates, RNCS, can be readily prepared by the rearrangement of the normal thiocyanates or by the action of sulfur on the isonitriles. They carry the name of *mustard oils* because the allyl compound, $CH_2=CHCH_2NCS$, is the active principle in mustard. All the alkyl isothiocyanates have a sharp odor and biting taste.

Many isothiocyanates, like the thiocyanates, are effective insecticides. The isothiocyanates have not come into general use as insecticides, however, because they are toxic or irritant to man and to plants.

Thiourea or Thiocarbamide. The sulfur analog of urea can be formed by melting the ammonium salt of thiocyanic acid; the reaction is parallel to Wöhler's classical synthesis of urea.

$$NH_4SCN \longrightarrow (NH_2)_2C = S$$

Thiourea is a crystalline compound melting at 180° and soluble in water.

Thiocarbanilide. Diphenylthiourea or thiocarbanilide, $S = C(NHC_6H_5)_2$, is one of the commonest organic sulfur compounds. It is prepared from aniline, $C_6H_5NH_2$; this is a primary amine which contains the phenyl group (C_6H_5) instead of an alkyl group. By heating carbon disulfide and aniline above 100°, the following reaction takes place.

$$2C_6H_5NH_2 + CS_2 \longrightarrow (C_6H_5NH)_2CS + H_2S$$

Thiocarbanilide is a crystalline solid melting at 154°. Its use as an accelerator of rubber vulcanization has been noted previously. The sulfur atom in diphenylthiourea may be replaced by the =NH group by heating the compound with lead oxide and ammonia. The product is a guanidine derivative containing two C_6H_5-groups, and hence is known as **diphenylguanidine**, $HN = C(NHC_6H_5)_2$. It has also been used in very large quantities as an accelerator in rubber vulcanization.

ORGANIC DERIVATIVES OF THE HYDRIDES OF OTHER ELEMENTS

We have noted that there are classes of organic compounds corresponding to the hydrides of nitrogen (NH_3), sulfur (H_2S), and oxygen (H_2O). Similarly, alkyl derivatives of the hydrides of many other elements are known. If we follow down the sixth group of the periodic table, we find organic compounds of selenium and tellurium quite comparable to the sulfur and oxygen compounds. In the fifth group of the table under nitrogen are phosphorus, arsenic, and antimony,

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and we might readily predict the existence of a variety of compounds analogous to the nitrogen compounds, but containing one of these elements in place of the nitrogen atom. Many such substances are indeed known. In general the differences among the organic compounds of these other elements and their more common prototypes (containing nitrogen or oxygen) reflect the differences among the elements themselves. With the exception of the zinc alkyls (p. 29) and the organomagnesium compounds (Grignard reagents), the organic chemistry of the elements other than oxygen, nitrogen, sulfur, and the halogens, is not of sufficient importance to warrant consideration in an elementary book.

QUESTIONS AND PROBLEMS

1. Write the equation for the reaction between carbon disulfide, an alcohol, and potassium hydroxide. Explain why this reaction is of such importance in the rayon industry.

2. What test would distinguish quickly between $CH_3CH_2SO_2ONa$ and $CH_3CH_2OSO_2ONa$?

3. Compare and contrast the acidic properties and the boiling points of the alkyl derivatives of water, ammonia, and hydrogen sulfide.

4. Write electronic formulas for a mercaptan, a sulfone, a sulfoxide, a sulfonamide, and a trialkylsulfonium bromide.

5. Devise a method of synthesizing BAL from propylene.

6. Indicate the tests you would use to differentiate between (*a*) $(CH_3O)_2SO_2$ and $CH_3SO_2OCH_3$, (*b*) C_4H_9SH and $(C_2H_5)_2S$.

7. Outline the steps in the synthesis of dimethyl disulfide, diethyl sulfone, methyl thiocyanate, methyl isothiocyanate (two methods), butanesulfonic acid (two methods).

8. β-Disulfones, such as $RSO_2CH_2SO_2R$ form sodium derivatives on treatment with sodium methoxide. Write the structure of the ion of such a metallic derivative.

9. How would you bring about the following transformations: (*a*) ammonium thiocyanate to thiourea, (*b*) ethyl sulfide to ethyl sulfoxide, (*c*) ethylene to mustard gas?

10. Using general equations illustrate a typical method of preparing each of the following classes of compounds: alcohols, mercaptans, ethers, sulfides.

11. Complete the reactions: (*a*) $(CH_3)_2CHSH$ + air, (*b*) $(CH_3)_2S + CH_3CH_2I$, (*c*) $CS_2 + NaOCH(CH_3)_2$, (*d*) $(CH_3)_2NH + CS_2 + NaOH$, (*e*) $(CH_3)_3SOH + HBr$, (*f*) $CH_3CHO + CH_3SH$.

12. Contrast the chemical properties of diethyl sulfide and diethyl ether. To what attribute of sulfur may this difference be ascribed?

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Chapter 19

THE AMINO ACIDS AND PROTEINS

Occurrence of Proteins. Fats, carbohydrates, and proteins are the three great classes of compounds which are of prime importance to the biologist and biochemist. We have already considered the first two of these classes and shall devote this chapter to the proteins alone. Proteins occur widely distributed in both plants and animals and are an essential constituent of foodstuffs. Both vegetable proteins and animal proteins occur as solids and in solution. The animal proteins are in part in solution in the body fluids, e.g., in the blood, but in larger part they are the insoluble materials of which the animal tissues are composed. Thus, skin, hair, muscle tissue, and the horny material of nails, horns, and hoofs are essentially proteins. The proteins serve as structural materials for animals much as the polysaccharides (e.g., cellulose) do for plants. Proteins, like fats and carbohydrates, may be used as a source of energy when they are consumed by animals. In plants, proteins are found in all the living parts but usually in relatively small quantities except in the seeds.

Relation of Proteins to Amino Acids. In their physical properties proteins differ widely from one another. The water-soluble material, white of egg, the partially soluble gelatine, and the insoluble hide of animals are all proteins. In one fundamental respect all proteins are similar—by boiling with dilute acid they are all hydrolyzed to a mixture of **alpha amino acids.** Twenty-four different amino acids have been isolated from the hydrolysis of a variety of proteins. These substances are the building blocks out of which the complex protein molecules are constructed. Therefore, before proceeding further we must consider briefly the amino acids themselves.

AMINO ACIDS

The amino acids are classified according to the relative positions of the amino group and carboxyl group. The nomenclature follows the same principle used with the halogen and hydroxyl derivatives of acids (p. 234). Thus **alpha aminobutyric acid** is $CH_3CH_2CHNH_2COOH$

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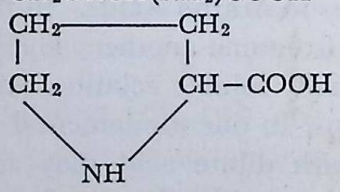
and **beta aminobutyric acid** is $CH_3CHNH_2CH_2COOH$. Fortunately, the amino acids which are formed by the hydrolysis of proteins are all of one class. They are alpha amino acids and we shall confine our attention to them.

Alpha Amino Acids from Proteins. The amino acids which have been isolated from the mixtures obtained by hydrolysis of a great variety of proteins are listed below for reference. The student is advised to familiarize himself with the special names and formulas of one or two representatives of each of the three groups into which the acids are divided. The special names are used in this field to the almost complete exclusion of a rational nomenclature.

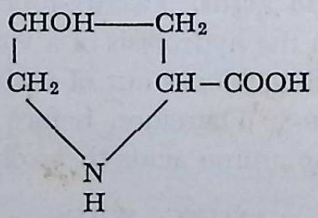
AMINO ACIDS OBTAINED BY THE HYDROLYSIS OF PROTEINS

A. Acids with equal number of basic and acid groups (one each except No. 17):

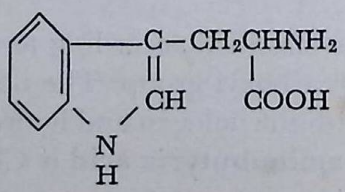
1. Glycine (Glycocoll): $CH_2(NH_2)COOH$
2. Alanine: $CH_3CH(NH_2)COOH$
3. Valine: $(CH_3)_2CHCH(NH_2)COOH$
4. Leucine: $(CH_3)_2CHCH_2CH(NH_2)COOH$
5. Norleucine: $CH_3CH_2CH_2CH_2CH(NH_2)COOH$
6. Isoleucine: $C_2H_5CH(CH_3)CH(NH_2)COOH$
7. Phenylalanine: $C_6H_5CH_2CH(NH_2)COOH$
8. Tyrosine: $p\text{-}HOC_6H_4CH_2CH(NH_2)COOH$
9. Threonine: $CH_3CHOHCH(NH_2)COOH$
10. Serine: $CH_2OHCH(NH_2)COOH$
11. Proline:



12. Hydroxyproline:



13. Tryptophane:



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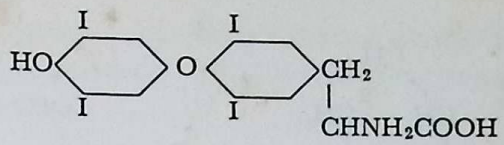
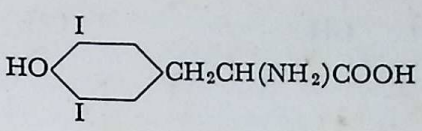
14. Thyroxine:



15. Iodogorgoic acid:



16. Methionine: $CH_3SCH_2CH_2CH(NH_2)COOH$

17. Cystine:

$$\begin{array}{l} SCH_2CH(NH_2)COOH \\ | \\ SCH_2CH(NH_2)COOH \end{array}$$

18. Cysteine: $HSCH_2CH(NH_2)COOH$

B. Basic Amino Acids (several basic groups and one acid group):

1. Lysine: $CH_2NH_2CH_2CH_2CH_2CH(NH_2)COOH$

2. Arginine:

$$\begin{array}{l} \qquad\quad NH_2 \\ \qquad\quad | \\ NH = C - NHCH_2CH_2CH_2CH(NH_2)COOH \end{array}$$

3. Histidine:

$$\begin{array}{l} CH = C - CH_2CH(NH_2)COOH \\ | \qquad\; | \\ N \qquad NH \\ \quad \diagdown \; \diagup \\ \quad\; CH \end{array}$$

C. Acid Amino Acids (several acid groups and one basic group):

1. Aspartic acid: $HOOCCH_2CH(NH_2)COOH$

2. Glutamic acid: $HOOCCH_2CH_2CH(NH_2)COOH$

3. β-Hydroxyglutamic acid:

$$\begin{array}{l} HOOCCH_2CHOHCHNH_2 \\ \qquad\qquad\qquad\quad | \\ \qquad\qquad\qquad\; COOH \end{array}$$

Heterocyclic and Aromatic Groups. The student will note that in several of the amino acids, he encounters for the first time special cyclic groups. In particular he will find in phenylalanine (A7), the phenyl group, C_6H_5-, encountered earlier in Buna S synthetic rubber, and in tyrosine (A8) the closely related hydroxyphenyl group, HOC_6H_4-. The structures of these two cyclic groups are:

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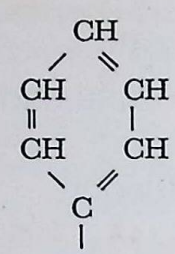
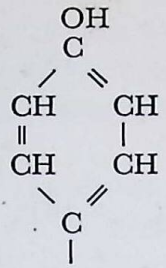


C_6H_5- Phenyl



HOC_6H_4- Hydroxyphenyl

We shall consider in Chaps. 21 to 27 the special chemistry of this type of unsaturated ring which is called an *aromatic ring*. The same ring occurs in thyroxine (A14) and iodogorgoic acid (A15). Still more complex unsaturated rings containing nitrogen are present in tryptophane (A13) and histidine (B3). Unsaturated rings have as a rule a somewhat special behavior which is of importance in the following ways in protein and amino acid chemistry: (1) the hydroxyl group in tyrosine, thyroxine, and iodogorgoic acid is more acidic than the hydroxyl group of an aliphatic alcohol; it is comparable with an enol; (2) the nitrogen atom in tryptophane has no basic properties; it is like the nitrogen of an amide; (3) one of the two nitrogen atoms in the unsaturated ring in histidine is basic, though less basic than a secondary amine. Other than this, however, in an elementary study of the amino acids and proteins the unsaturated cyclic groups can be regarded as somewhat complicated alkyl groups. The presence of saturated rings in proline (A11) and hydroxyproline (A12) should present no difficulties to the student: the nitrogen atom acts very much as it would were it in an open-chain secondary amine.

Classification. The alpha amino acids have been classified above according to the relative number of acid and basic groups in the molecule. The importance of this relationship from the point of view of the behavior of the substances will soon become apparent. Although tryptophane has a cyclic $>$NH group in addition to the alpha amino group, it is placed in group A because the second nitrogen atom has no basic properties. On the other hand, the $>$NH groups in the saturated rings in proline (A11) and hydroxyproline (A12) and in the heterocyclic ring in histidine (B3) are basic. The hydroxyl group in tyrosine is weakly acidic; if this group is counted as an acid group, tyrosine would be put in class C.

With the exception of glycine (α-aminoacetic acid) all the alpha

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amino acids contain one or more asymmetric carbon atoms. Therefore, as would be expected, those amino acids which are prepared from proteins are optically active.

In the isolation of amino acids from protein hydrolysates, advantage is taken of the separation into groups according to the solubility of the acids and their salts. The acids in group A are, with the exception of tyrosine (8) and the closely related iodine compounds (14 and 15), all very soluble in water but insoluble in anhydrous alcohol. They may be extracted from their aqueous solutions with *n*-butyl alcohol by continuous extraction (the butyl alcohol layer is saturated with water). When the butyl alcohol solution is rendered water-free by distilling a portion of the alcohol which carries the water with it, all the acids, except proline and hydroxyproline, crystallize from the solution. The separation of this mixture into its constituents is difficult. Of the amino acids which are not extracted by butyl alcohol, those of group B form insoluble salts with phosphotungstic acid and can thus be precipitated by this reagent. The further separation of the acids of this class and those of class C usually depends on the differential solubility of certain salts in different solvents.

Synthesis of Alpha Amino Acids. There are several important methods of synthesizing alpha amino acids in the laboratory. The corresponding simple acid may be halogenated in the alpha position by the action of chlorine or bromine on the acid or the acid chloride. We have already met this reaction in the preparation of chloroacetic and alpha chloropropionic acids (p. 100). On treatment with ammonia, alpha chloro or bromo acids readily yield alpha amino acids.

$$CH_2ClCOOH + 2NH_3 \longrightarrow CH_2NH_2COOH + NH_4Cl$$

Another method of synthesis starts with an aldehyde. This is treated in an aqueous or alcoholic solution with sodium cyanide and ammonium chloride. Solutions of a cyanide always contain considerable free hydrocyanic acid from hydrolysis (hydrocyanic is a very weak acid), and this hydrocyanic acid adds to the aldehyde forming a cyanohydrin (p. 136).

$$RCHO + HCN \longrightarrow RCHOHCN$$

The alkali formed by the hydrolysis ($NaCN + H_2O \rightleftharpoons NaOH + HCN$) liberates ammonia from the ammonium chloride, and this reacts with the cyanohydrin.

$$RCHOHCN + NH_3 \longrightarrow RCHNH_2CN + H_2O$$

The amino cyanide, $RCHNH_2CN$, is thus directly formed by the interaction of the aldehyde and the two inorganic substances. The alpha amino cyanide may be hydrolyzed to an alpha amino acid by boiling with dilute acid.

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Finally, the preparation of alpha amino acids by the reduction of alpha ketonic acids in the presence of ammonia should be mentioned.

$$RCOCOOH + NH_3 + 2[H] \longrightarrow RCH(NH_2)COOH + H_2O$$

Amino Acids as Inner Salts. The amino acids have both basic and acidic properties; when treated with mineral acids or strong bases they form crystalline salts in which the organic residue is the cation or the anion. The neutral molecule itself is in a sense a salt for the hydrogen atom of what would be the carboxyl group is joined to the basic nitrogen atom. Thus the correct formula for an amino acid is $\begin{array}{l} RCHNH_3^+ \\ | \\ COO^- \end{array}$. This inner formula corresponds to the physical and chemical properties of the amino acids.

$$\begin{array}{l} RCHNH_3Cl \\ | \\ COOH \end{array} \underset{NaOH}{\overset{HCl}{\rightleftharpoons}} \begin{array}{l} RCHNH_3^+ \\ | \\ COO^- \end{array} \underset{NaOH}{\overset{HCl}{\rightleftharpoons}} \begin{array}{l} RCHNH_2 \\ | \\ COONa \end{array}$$

The total net electrical charge on the organic molecule will clearly depend on the acidity of the solution. In acid solution the amino acid will be present as a positive ion, $RCHNH_3^+COOH$, in alkaline solution as a negative ion, $RCHNH_2COO^-$, and at a certain acidity the *net* charge will be zero since the molecule has the structure $RCHNH_3^+COO^-$. In acid solutions, the amino acids migrate to the cathode (−) when the solutions are electrolyzed; in alkaline solutions, the molecules move to the anode (+). At a definite hydrogen ion concentration, when the net charge is zero, the compound moves neither to the cathode nor to the anode. This point is known as the *isoelectric point*. Its value depends on the relative strengths and number of acid and basic groups in the amino acid molecule.

Dipolar Ions. If one recalls the relation between the physical properties and the polar nature of a molecule (p. 71), it is not surprising to find that organic molecules which are inner salts are in a class by themselves. We may speak of such molecules as dipolar ions. The amino acids and proteins are by far the most important examples. The amino acids, though of low molecular weight, are nonvolatile solids. This means that the forces holding the molecules to each other are very large; indeed, they are comparable with the forces holding the ions together in salts. Many amino acids are not only nonvolatile solids, but they even decompose before melting—additional evidence of the

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strong forces holding the crystal lattice together. They are extremely insoluble in all nonpolar solvents (such as hydrocarbons) and are relatively far more soluble in water or salt solutions. Many of them will form quite concentrated solutions in water. This is so because they greatly increase the dielectric constant of the solution, which in turn means that the dipolar ions are more soluble. The very great importance of these phenomena will be evident when we consider the proteins.

We have already noted that an amino acid at its isoelectric point will not migrate in an electric field. The molecule, however, does tend to orient itself so that the electric dipoles line up in the field. This is the reason why solutions of dipolar ions have very high dielectric constants. How great this effect can be may be illustrated by the fact that a concentrated solution of glycine (about 3 molar) has a dielectric constant nearly twice that of water.

Reactions of Amino Acids. As would be expected, the α-amino acids show the characteristic reaction of both organic acids and primary aliphatic amines. They are readily esterified in the usual manner and the esters may be purified by distillation. This fact may be taken advantage of in the separation of the acids of group A. The reaction with nitrous acid liberates nitrogen and forms an hydroxy acid (p. 189). This is the basis of a convenient quantitative method used in studying amino acids and proteins.

$$RCHNH_2COOH + HNO_2 \longrightarrow RCHOHCOOH + N_2 + H_2O$$

Another method used in determining amino acids depends on the reaction between formaldehyde and the primary amino group. The resulting compound is not basic and the acid can be titrated as a weak acid.

$$\begin{array}{l} RCHCOOH \\ \quad\;\; | \\ \quad NH_2 \end{array} + CH_2O \longrightarrow \begin{array}{l} RCHCOOH \\ \quad\;\; | \\ \quad N = CH_2 \end{array} + H_2O$$

Creatine. $NH_2C(=NH)N(CH_3)CH_2COOH$. In addition to the amino acids which have been obtained from the hydrolysis of proteins (listed above), a few others also occur in nature. The most important of these is creatine, which may be regarded as derived from glycine since it contains the chain $N-CH_2COOH$.

Creatine is present in muscle tissue partially free and partially combined (amide linkage) with the phosphoric acid group. Creatine phosphoric acid together with adenylic acid pyrophosphate (p. 386) are involved in the changes which take place during contraction and relaxation of muscle.

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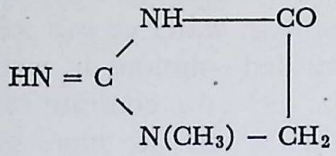
Small amounts of creatine are normally excreted in the urine in the form of the cyclic compound **creatinine.**



Creatinine also occurs widely distributed in plants; it is easily formed from creatine by warming an aqueous solution containing a little mineral acid. When treated with alkali, creatinine forms the salt of creatine. We are here dealing with the opening and closing of a ring very similar to that which occurs in lactones (p. 240).

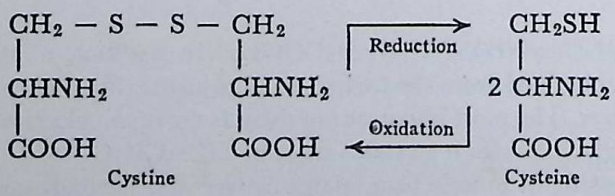
Ornithine. Another alpha amino acid, not itself a product of protein hydrolysis but closely related to one of the twenty-four acids, is α, δ-diaminovaleric acid, $NH_2CH_2CH_2CH_2CH(NH_2)COOH$, known as *ornithine.* It is produced in the liver by the hydrolysis of arginine by the enzyme **arginase.** It has been shown that ornithine goes through a cyclic process by which the liver synthesizes urea from ammonia and carbon dioxide. Each step is brought about by an enzyme but only the last step can be brought about outside the intact cell by an enzyme preparation.

$$NH_3 + CO_2 + \underset{\text{Ornithine}}{NH_2(CH_2)_3CH(NH_2)COOH} \longrightarrow \underset{\text{Citrulline}}{NH_2CONH(CH_2)_3CH(NH_2)COOH} + NH_3 \longrightarrow$$

$$\underset{\text{Arginine}}{NH_2C(=NH)NH(CH_2)_3CH(NH_2)COOH} \xrightarrow{+H_2O} \text{urea} + \text{ornithine}$$

Although we have no information as to the way the plant or animal cells synthesize the various amino acids, it is interesting to note the close relationship of arginine to histidine (ring closure with loss of hydrogen and ammonia) and of ornithine to proline (ring closure with loss of ammonia). Hydroxyproline is obviously closely connected. Tryptophane may be considered as N-phenylornithine in which ring closure and dehydrogenation have taken place. Thus, the ornithine skeleton $N - C - C - C - CH(NH_2)COOH$ occurs in arginine, histidine, tryptophane, proline, and hydroxyproline. Glutamic and hydroxyglutamic acids contain the same carbon skeleton but no second nitrogen atom.

Cysteine and Cystine. Cystine is a disulfide (p. 345) which on reduction readily forms two molecules of cysteine, which contains the mercaptan group. On oxidation cysteine forms cystine.



Other Related Substances. The decarboxylation of the amino acids results in the formation of a variety of nitrogenous bases. The

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process occurs in nature during putrefaction and decay. Thus arginine (by way of ornithine) yields putrescine, $NH_2(CH_2)_4NH_2$ (p. 195). Skatole, β-methylindole, a substance with a very disagreeable odor, is formed from tryptophane. By a bacterial decomposition, tryptophane is also degraded to β-indole acetic acid which is present in urine. β-Indole acetic acid is important in plant biochemistry as it is a growth-regulating substance for plants. For this reason it is classified as one of the **plant hormones** and is known as *heteroauxin*.

Glycine is frequently found in the form of its acyl derivatives. The glycocholic acid of bile (p. 587) is one example. Benzoyl glycine or **hippuric acid,** $C_6H_5CONHCH_2COOH$, found in the urine of horses, is another.

Betaine is a derivative of glycine in which the nitrogen atom has been converted into a quaternary ammonium salt by complete methylation. The inner salt formula of this compound follows from its structure. The fact that in its physical properties it is very similar to the amino acids is evidence for the correctness of formulating amino acids as dipolar ions.

$$(CH_3)_3\overset{+}{N}CH_2\overset{-}{COO}$$

Betaine

Since betaine is an inner salt of a strong base and a weak acid (a substituted acetic acid), it will form a hydrochloride, $[(CH_3)_3\overset{+}{N}CH_2COOH]Cl^-$, but not a sodium salt. In the hydrochloride the ionization of the weak acid has been suppressed by the mineral acid. Betaine occurs widely distributed in plants and has also been found in animal tissue. It can be obtained from the residues of beet-sugar molasses or prepared synthetically by methylating glycine. It is a crystalline solid with a very high melting point (like glycine itself); it is very soluble in water from which it crystallizes with a molecule of water of crystallization. It is interesting to note that choline (p. 196) is the primary alcohol corresponding to betaine.

PEPTONES AND POLYPEPTIDES

Proteins are completely hydrolyzed to amino acids by boiling for several hours with 10 per cent sulfuric acid or 30 per cent hydrochloric acid. The decomposition is also brought about by **enzymes.** These are involved in the digestion of proteins. **Pepsin** is present in the stomach and acts in a somewhat acid solution; **trypsin,** which occurs in the pancreatic juice, and **erepsin,** in the intestines, are involved also in the complete disintegration of the complex molecule. Each animal undoubtedly resynthesizes from the individual amino acids the particular proteins which constitute its tissue.

By studying the action of the proteolytic enzymes which can be

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isolated from living tissue, it has been possible to obtain mixtures of substances which are intermediate between proteins and amino acids. These are known as *proteoses* and *peptones*. They are water-soluble materials; unlike most proteins they do not coagulate on heating. Their molecules must be a great deal smaller than those of the proteins but they are still complex substances.

The synthetic work of Emil Fischer[1] showed that the proteoses and peptones are built up of many molecules of amino acids joined by the amide linkage, $-\overset{\overset{\displaystyle O}{\|}}{C}-NH-$. Fischer synthesized substances which he called *peptides*. The simplest is **glycyl-glycine,** $CH_2NH_2CONHCH_2COOH$; this is a **dipeptide.** A more complicated example is **leucyl-glycyl-glycine,** a **tripeptide.**

$$(CH_3)_2CHCH_2\underset{\underset{\displaystyle NH_2}{|}}{CH}\overset{\overset{\displaystyle O}{\|}}{C}-NHCH_2\overset{\overset{\displaystyle O}{\|}}{C}-NHCH_2COOH$$

The most complicated peptide that he prepared was composed of eighteen molecules of amino acids (fifteen of glycine and three of leucine). This substance had a molecular weight of 1213 and in its general behavior was very similar to the natural peptones and proteoses. This polypeptide was even hydrolyzed by the enzymes, trypsin and erepsin. When it is recalled that the action of enzymes is very specific, it is clear that this fact is important evidence for the similarity between the synthetic material and the partial decomposition products of proteins.

A consideration of the structure of a peptide makes it evident why these substances can be hydrolyzed. The reaction is exactly like the hydrolysis of an amide (p. 179) and like this process is catalyzed by hydrogen or hydroxyl ions.

The Synthesis of Polypeptides. Fischer employed a number of closely related methods in his synthesis of complex polypeptides. Two examples only will be given. The acid chloride of an alpha halogen acid can be readily prepared from the alpha halogen acid (see also p. 100). If this substance is treated with an amino acid, the following reaction takes place.

[1] See p. 285. Fischer's principal work on proteins was during the period 1899–1906. A very large part of our knowledge concerning monosaccharides, proteins, and tannins is due to his extraordinary genius.

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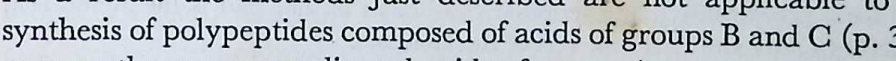
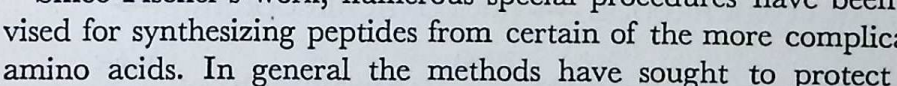


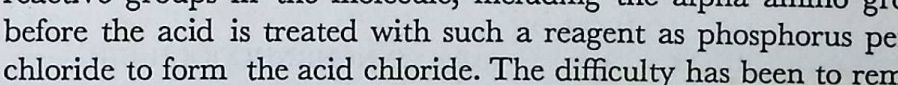
$$ClCH_2COCl + H_2NCH_2COOH \longrightarrow ClCH_2CONHCH_2COOH$$

On treating the product with ammonia, a dipeptide is formed.



$$ClCH_2CONHCH_2COOH + 2NH_3 \longrightarrow CH_2NH_2CONHCH_2COOH + NH_4Cl$$

The acid chlorides of the amino acids themselves are very difficult to prepare. These acid chlorides will react with an amino acid, producing a dipeptide, or with a dipeptide, forming a tripeptide. An example of the latter reaction would be the preparation of glycyl-glycyl-glycine.



$$CH_2NH_2COCl + H_2NCH_2CONHCH_2COOH \longrightarrow CH_2NH_2CONHCH_2CONHCH_2COOH$$

It is evident that by repeating either of these two methods a molecule may be constructed containing many of the simple amino acid residues. However, the preparation of acid chlorides of amino acids containing other reactive groups, such as hydroxyl, is not possible. As a result the methods just described are not applicable to the synthesis of polypeptides composed of acids of groups B and C (p. 355) or even the more complicated acids of group A.

Since Fischer's work, numerous special procedures have been devised for synthesizing peptides from certain of the more complicated amino acids. In general the methods have sought to protect the reactive groups in the molecule, including the alpha amino group, before the acid is treated with such a reagent as phosphorus pentachloride to form the acid chloride. The difficulty has been to remove these protecting groups after the peptide has been synthesized without hydrolyzing the peptide link. The use of the **carbobenzyloxy group,** $C_6H_5CH_2OCO-$ (also called a *carbobenzoxy group*) has recently been introduced with great success. An acid chloride which is also an ester and which is known as *carbobenzoxy chloride* has the formula $C_6H_5CH_2O\overset{\overset{O}{//}}{C}-Cl$. This substance readily reacts with amino compounds replacing one hydrogen atom by the $C_6H_5CH_2OCO-$ group. This protecting group may be removed when desired by catalytic hydrogenation or by reduction with metallic sodium in liquid ammonia. A simple example of the use of the carbobenzyloxy group is as follows:

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$$C_6H_5CH_2OC(=O) - Cl + H_2NCH_2COOH \longrightarrow$$

$$C_6H_5CH_2OCONHCH_2COOH \xrightarrow{PCl_5} C_6H_5CH_2OCONHCH_2COCl$$

$$\xrightarrow{RCHNH_2COOH} C_6H_5CH_2OCONHCH_2CONHCHRCOOH$$

$$\xrightarrow{2[H]} C_6H_5CH_3 + CO_2 + NH_2CH_2CONHCHRCOOH$$

Degradation of Peptide Chain. Polypeptides are hydrolyzed to the constituent amino acid by heating with acids or by the action of various enzymes. Complete hydrolysis, although it reveals the amount of each amino acid combined in the peptide, obviously gives no information as to the order in which the components are linked. Thus leucyl-glycyl-alanine and glycyl-alanyl-leucine would yield identical mixtures of amino acids on hydrolysis. Stepwise hydrolysis is sometimes possible by means of enzymes, and important information can often be obtained in this manner. A general procedure has been developed taking advantage of the Curtius reaction of the acid azides (p. 335) and of the cleavage of the carbobenzyloxy linkage by reduction. Each constituent amino acid residue can be removed from a peptide chain step by step in the form of the *corresponding aldehyde* (which is identified by the usual method). The fundamental reactions may be illustrated by letting (AR)CONHCHRCOOH stand for a polypeptide whose terminal constituent on one end is the amino acid $RCHNH_2COOH$ and (AR) the rest of the molecule.

$$(AR)CONHCHRCOOH \longrightarrow (AR)CONHCHRCOOC_2H_5 \xrightarrow{NH_2NH_2}$$

$$(AR)CONHCHRCONHNH_2 \xrightarrow{HNO_2} (AR)CONHCHRCON_3 \xrightarrow{\text{Heated}}$$

$$\underset{\text{Not isolated}}{(AR)CONHCHRNCO} \xrightarrow{C_6H_5CH_2OH} (AR)CONHCHRNHCOOCH_2C_6H_5 \xrightarrow{2H}$$

$$(AR)CONHCHRNH_2 \xrightarrow{\text{Hydrolyze}} (AR)CONH_2 + RCHO + NH_3$$

In practice the terminal free amino group of the peptide is first converted into the C_6H_5CONH- group by treating the peptide with benzoyl chloride; other reactive groups would have to be protected also. The final cleavage depends on the fact that a compound of the type $RCH\begin{matrix}NH_2\\NHCOR\end{matrix}$ on hydrolysis would yield a compound with two amino groups on the same carbon atom. Such substances, like those which might have two hydroxyl groups (p. 146), are unstable and in aqueous solution yield ammonia and an aldehyde. The other product of the reaction, an acid amide, may be

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converted into the azide required for the next step of the degradation by treating with hydrazine (replacement of $-NH_2$ by $-NHNH_2$) followed by nitrous acid.

Degradation of glycyl-alanyl-leucine by this procedure yields in the first step, isovaleric aldehyde and in the second, acetaldehyde and glycine (as the benzoyl compound).

PROTEINS

In considering the structure of the proteins, it is convenient to recognize at the outset two large subdivisions of this great class of naturally occurring compounds. In one group we may place those fibrous insoluble proteins such as constitute the major part of wool, hair, silk, and the connective tissues of animals. In the other we may place all the other plant and animal proteins which are soluble without decomposition in either water, water-alcohol mixtures, dilute aqueous salt solutions, or dilute aqueous alkali or acid. The substances in both classes are clearly of very high molecular weight and on hydrolysis are completely broken down to a mixture of amino acids.

The differentiation of proteins into these two groups corresponds, as we shall see, not only to very different physical and chemical properties (e.g., solubility) but to a somewhat different composition and to a different shape of the molecule.

A few proteins, like myosin of muscle, have properties intermediate between those of the two main subdivisions just mentioned. Myosin is composed of very long fibrous elements, but it dissolves easily in moderately concentrated salt solutions and is precipitated from such solutions when they are diluted.

Keratin and Fibroin. Hair and silk are nearly pure proteins; the former is known as *keratin*, the latter as *fibroin*. They dissolve only in strong acids and bases and are at least partially decomposed under these conditions. They are insoluble in all of the ordinary solvents; the usual methods of organic chemistry, therefore, are not available for investigating their structure. The use of physical methods has, however, thrown much light on the structure of these proteins. By using essentially the same technique as is employed in determining the structure of crystals by X-ray diffraction, it was shown that fibroin and keratin molecules contain a recurring pattern of atomic centers. These, we have every reason to believe, are the characteristic recurring links of the peptide chain. The keratin and fibroin molecules are thus composed of very long peptide chains just as the cellulose molecule (p. 296) is composed of a long chain of connected cellobiose

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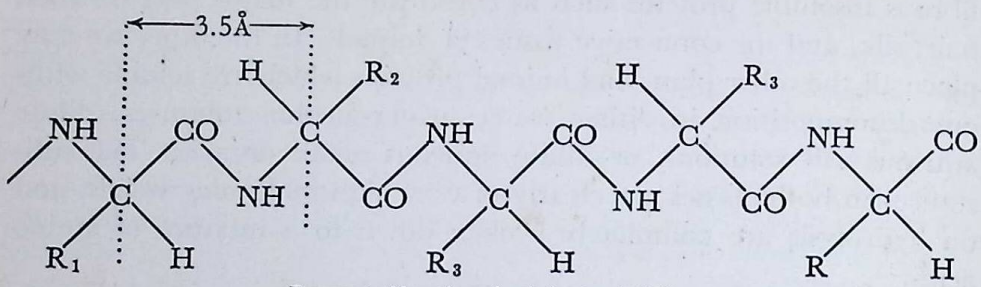
molecules. Certain of the protein fibers show two different X-ray patterns according to whether they are stretched or unstretched. The distances between recurring centers is much greater in the stretched form. This indicates that in the normal fiber the chain is somewhat coiled by virtue of attraction, perhaps, between alternating CO and NH groups. This would bring the side chains represented by R_1R_2 (below) nearer together. It is the recurring pattern of these branches which produces the characterisitic X-ray diffraction. The distance between CHR groups in the extended chain is 3.5Å according to the



Fragment of keratin molecule in stretched fiber

X-ray measurement. This is practically identical with the distance calculated from the known internuclear distances of the normal C – C (1.54Å) and the C – N links (approx. 1.4Å), assuming a valence angle of both links of 109° 28′.

The intermolecular forces between the large molecules are very considerable in the proteins since the $-\overset{\overset{\displaystyle O}{\|}}{C}-NH-$ group which recurs is of a partially polar type. Therefore the cohesive force between the chains is usually greater than the force between the same group and water. Most proteins are insoluble in pure water.

Composition of Fibrous Proteins. The amino acids obtained from the hydrolysis of the inert insoluble proteins such as silk, hair, wool, and hide are largely those of group A (p. 354). This means that the side chains (R_1, R_2, R_3, etc.) extending away from the polypeptide chain are chemically inert. Fibroin (silk) is composed almost entirely of glycine, alanine, and tyrosine. The amino acids of group C are absent and only very small quantities of arginine and lysine (class B) are present. Keratin from wool contains a larger percentage of the basic amino acids. On hydrolysis of keratin (wool), glutamic acid (class C) is also formed in considerable amounts, but so is free ammonia. This indicates that almost all of the COOH groups in the

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side chain of *d*-glutamic acid are present as neutral amide groups $-CONH_2$. The insolubility of the fibrous proteins in dilute aqueous acids and bases is thus explained by the absence of any large number of acid or basic groups in the side chains.

Classification of Other Proteins. Leaving aside the inert proteins we have just been considering, we may classify the others by their solubility relations. This is a rough, empirical, but useful classification, and we shall see that it is not unrelated to the preponderance of one type of amino acid or another in the molecule.

1. Albumins: Soluble in water and dilute salt solutions. **Egg albumin** (white of egg) is an example.

2. Globulins: Insoluble in water but soluble in dilute solutions of neutral salts. The vegetable protein, **edestin** (from hemp seed), and the animal protein, **serum globulin** (in the blood serum), are two examples of this class.

3. Glutelins: Insoluble in water or dilute neutral salt solutions. Soluble in alkaline or acid solution. **Glutenin,** which occurs in wheat, is a representative.

4. Prolamines: Insoluble in water or dilute salt solutions. Soluble in 80 per cent alcohol. All the representatives of this class are vegetable proteins. **Zein** occurs in corn, **gliadin** in wheat.

5. Histones and Protamines: Basic proteins, soluble in water and acids. The two classes are usually separated on the basis of the insolubility of histones in ammonia. Protamines occur in ripe fish sperm.

In some classifications, fibroin, keratin, and the other fibrous proteins are classified as a sixth group, **albuminoids.** The name which suggests some relation to the albumins is, however, unfortunate.

Acid and Basic Properties. A large number of the proteins are amphoteric substances, that is they combine with acids or bases forming water-soluble salts. This process is strictly reversible unless very strong acid or alkali is employed; this may alter (denature) the protein. The globulins and glutelins which are insoluble in water dissolve in dilute acid or basic solution because they form water-soluble salts.

Like the amino acids, each amphoteric protein will migrate during electrolysis of the solution to either the anode or cathode, depending on the acidity of the medium. The **isoelectric point** at which no migration takes place is an important characteristic of each protein.

In general, proteins are least soluble *near* their isoelectric point. Therefore, in "salting out" proteins or precipitating water-insoluble

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proteins, care is taken to bring the acidity of the solution to the proper value. For egg albumin this is a hydrogen ion concentration of 15×10^{-6}; for hemoglobin, 2×10^{-7}. It will be recalled that pure water has a hydrogen ion concentration of 1×10^{-7}.

In addition to the amphoteric proteins, there are others in which either the acid or basic properties are especially pronounced. The **protamines** which occur in fish sperm are an example of a basic protein. **Zein,** the protein of corn, is just the reverse; it reacts with bases but only to a slight extent with acids. Zein contains very few basic groups per molecule, and will dissolve in alkaline solution but not in acids.

The Significance of Acid and Basic Amino Acids. If the protein molecules were composed only of the amino acids listed in class A of our tabulation (p. 354), they would be neutral substances without acid or basic properties. An approach to this condition is found in keratin and fibroin. If a large proportion of the constituent amino acids were of class C, the side chains would carry carboxyl groups. Unless these groups were present as amides (as in wool), the protein should be able to form salts with bases. The presence of a large proportion of basic amino acids (group B) in a protein should enable it to form salts with acids. If, however, representatives of both class B and C were present in goodly number, the large molecule should be amphoteric. This is the case with egg albumin, for example, which contains about 10 per cent of basic amino acids and about 15 per cent of acidic amino acids (class C). An examination of the amino acids formed by hydrolysis has shown that *the acid and base binding capacity of different proteins is determined by the nature of the amino acids of which their molecules are composed.*

A few examples will make this clear. Zein, which is so little basic that it will not dissolve in acids, contains an extremely small amount of basic amino acids. The protamines, which are basic, yield on hydrolysis large amounts of amino acids with basic groups (class B). Quantitative experiments have shown that casein neutralizes twice as much sodium hydroxide as it does hydrochloric acid. The composition of this amphoteric protein corresponds closely with this relationship; it yields about twice as many molecules of the acid amino acids (class C) as basic amino acids (class B). Thus the amino acids with extra basic or acid groups are of fundamental importance in determining the behavior of proteins.

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Purification of Proteins. The method of purifying proteins is based on their solubility. All proteins are insoluble in a concentrated salt solution such as saturated ammonium sulfate. Water-soluble proteins, therefore, may be "salted out" by the addition of solid ammonium sulfate. The precipitate redissolves on treatment with pure water. A number of proteins have been obtained in the crystalline condition by careful regulation of the hydrogen ion and salt concentration of saturated solutions. The recrystallization of such proteins is the best method of purification. The crystals are kept moist throughout the procedure as drying alters most soluble proteins to some extent.

During World War II the many important soluble proteins in blood plasma were separated with great success by precipitation at 0° to −10° with organic solvents such as ethyl alcohol. By varying the salt concentration of the aqueous solution, the acidity, the temperature, the alcohol concentration, and the total protein concentration in a systematic fashion the separation of sensitive proteins has been done on a large scale. The alcohol can be removed in a vacuum at low temperature, whereas, if salt is used as a precipitant, it can only be removed by a tedious dialysis.

Irreversible Precipitation of Proteins. The reversible precipitations just mentioned are very different from the *irreversible precipitation* of proteins which is brought about by a number of reagents such as **trichloroacetic acid, tannic acid, picric acid, concentrated nitric acid,** and **phosphotungstic acid.** The mercury, lead, and copper salts of proteins precipitate when soluble salts of these metals are added to protein solutions. This is also essentially an irreversible process as the original protein cannot be obtained from these precipitates. The precipitation of proteins by such reagents is useful in testing for proteins or removing them from a solution but cannot be used in purification as the process in some way alters the material.

The majority of water-soluble proteins are precipitated when their solutions are heated. This process is irreversible. The "cooking" of white of egg is a common example of the **heat coagulation** of a protein.

Molecular Weights of Proteins. Even the water-soluble proteins are substances of very high molecular weight. The usual direct methods of determining molecular weight, for example, by the observation of the freezing point of solutions of known concentration cannot be employed. With substances of large molecular weight the

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depression is too slight to be measured accurately and the presence of even small quantities of inorganic impurities would vitiate the result. Some determinations of the osmotic pressure of protein solutions have given fairly satisfactory information about the molecular weights, but the most reliable method depends on the use of the ultracentrifuge. In this procedure a solution of the substance of high molecular weight is spun at very high speeds. The centrifugal force thus generated moves the dissolved molecules away from the center. While the container is still being rotated at the desired speed the concentration gradient from the center to the outside edge is determined by a photographic method. Knowing the speed, the dimension of the ultracentrifuge, and the change in concentration of the protein solution throughout the revolving container, it is possible to calculate the molecular weight. Some of the results obtained are given below.

MOLECULAR WEIGHTS OF SOME PROTEINS

Lactalbumin	17,500	
Gliadin	27,000	
Zein	50,000	
Insulin	46,000	
Egg Albumin	43,000	(By osmotic pressure, 45,000)
Hemoglobin	68,000	(Same value by osmotic pressure)
Serum albumin	68,000	(By osmotic pressure, 70,000)
Serum globulin	167,000	(By osmotic pressure, 156,000)
Phycocyan	272,000	
Edestin	309,000	
Hemocyanin	8,900,000	

In solution the proteins are probably present in more or less spherical globular form. When they are distributed as a thin film, however, on the surface of a liquid, the soluble proteins appear to approach the condition of the fibrous proteins; the molecules then consist of parallel, extended, polypeptide chains.

Denaturation. Perhaps the most characteristic property of the soluble proteins is the ease with which they undergo a change known as *denaturation*. A denaturated protein is less soluble than the normal (or native) protein and it will not crystallize. Drying, treatment with rather concentrated acid or alkali, and the addition of alcohol to an aqueous solution at room temperature, denature many proteins; a concentrated solution of urea is also an effective agent for bringing about denaturation. The rate of denaturation increases rapidly with

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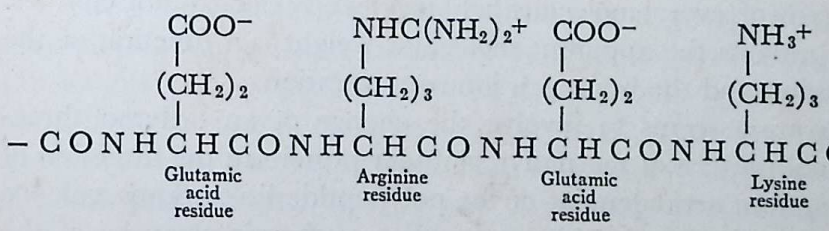
increase in temperature. Therefore many solutions of proteins can be kept for long periods of time at 0° but are rapidly denatured at 50° to 60°. The ease with which many proteins are thus altered makes the manipulation of this class of substances peculiarly difficult. The techniques employed with proteins are, therefore, quite different from those used with most organic compounds.

The coagulation of protein solutions on heating and the precipitation with many reagents, such as metallic salts and tannic acid, are examples of extreme denaturation. Certain proteins, if denatured by relatively mild reagents, can be slowly restored to the native state by dissolving in alkali and then adjusting the hydrogen ion concentration to a proper value. Measurements of the molecular weight by the osmotic pressure method indicate that in a number of instances there is no change in the molecular weight on denaturation. With a few proteins of very high molecular weight, denaturation appears to involve a dissociation of the molecule into as many as six parts.

Structure of Soluble Proteins. The presence of a considerable number of basic and acid amino acids (groups B and C) in a protein molecule must mean that many side chains carry electric charges. The acidic and basic groups interact to form salts by transfer of a proton. Thus, a hypothetical fragment of a protein molecule containing considerable amounts of lysine, arginine, and glutamic acid might be represented as follows:



The existence of many electric dipoles on a chain must modify enormously the forces involved in the arrangement of the chain in three dimensions. Furthermore a large molecule carrying these charges has unusual properties; it is a strong dipole for the following reasons: (1), there may be many inner salt groups per molecule; and, (2), the distance between the electric charges may be much greater than in the amino acids. (The influence of this last effect is noted with the di- and tripeptides of glycine which increase the dielectric constant of water more than does glycine.)

In general terms one may say that polar compounds (including

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dipolar ions) are more soluble the higher the dielectric constant of the medium. From this point of view, the solubility of the albumins (class 1, p. 367) in pure water is to be attributed to the fact that they contain many dipoles per molecule, and the increase in the dielectric constant of the solution tends to make further material more soluble; in addition the relatively low molecular weight as compared to many other proteins and the relative weakness of the intermolecular forces undoubtedly play a part. In the globulins, the intermolecular forces are sufficient to prevent solubility in pure water; but in salt solutions with higher dielectric constant (and certain specific effects) the dipolar ions dissolve. Solutions of proteins at the isoelectric point or in more acidic or basic solutions are solutions of large molecules with electric charges at many points. This means that all such solutions have high dielectric constants; they consequently are good solvents for salts and other dipolar ions. This fact has enormous consequences for biology and for those who work with proteins in the laboratory.

It seems probable that in the globular form in solution, the polypeptide chain is folded into some network. Whether, in the folding of a chain into a globular form, real covalence forces are involved is still a matter of discussion. It has been suggested that six-membered rings are formed by cyclization of the CO group with the NH group twice removed along the chain. The dissolved protein molecule is also probably heavily hydrated. Some of the larger protein molecules may be aggregates of several molecules held together by electrostatic charges. In some proteins the apparent molecular weight is a function of the concentration and the hydrogen ion concentration.

Denaturation seems to involve the change of an ordered three-dimensional pattern of the native globular protein in the direction of a more random arrangement of the polypeptide links. Some valence bonds may be broken in this process but no drastic cleavage of the polypeptide chain is involved.

Although synthetic work established the fact that the proteoses are polypeptides (p. 362), the difference in behavior and molecular weight between these compounds and proteins led some chemists to believe that other types of linkages were characteristic of proteins. All the evidence accumulated in recent years, however, indicates that the polypeptide chain is the essential element in the structure of even the giant molecules of a protein. It has been established, for example, that some of the enzymes which hydrolyze native proteins are also effective in hydrolyzing synthetic peptides. They attack preferentially

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the interior peptide links. Thus, the enzymatic hydrolysis of a protein seems to involve only the hydrolysis of the — CONH — bond.

Conjugated Proteins. A totally different method of classifying proteins from the one we have been using is sometimes employed. Proteins are divided into simple proteins, which yield only amino acids on hydrolysis; and others, called *conjugated proteins*, in which some other component is linked to the protein. The nonprotein portion is called a **prosthetic group.** If the group confers color on the protein, as in hemoglobin and the colored proteins present in algae (**phycocyan**), the protein may be known as a *chromoprotein.* If the prosthetic group is a carbohydrate the substance is a **glucoprotein.** Glucoproteins are found in mucous secretion. **Casein** (from milk) is often classed as a **phosphoprotein** as the prosthetic group contains phosphoric acid. The **nucleoproteins** contain a nucleic acid (p. 617) residue linked to the protein molecule. When the prosthetic group is colored it is easily recognized. In some proteins, e.g., hemoglobin, the prosthetic group is attached by a linkage that may be attacked by certain reagents without hydrolyzing the protein. If the prosthetic group is joined by an amide linkage, it may not be possible to separate it from the rest of the molecule without drastic decomposition of the protein. There may be a number of prosthetic groups (i.e., residues other than amino acids) which have not yet been isolated and identified from well-known proteins.

Virus Proteins. The filterable viruses are a group of nucleoproteins of great importance. In spite of their very high molecular weight (15,000,000 to 20,000,000), some of the filterable viruses have been isolated in crystalline condition by the usual procedures of protein chemistry. They are responsible for the transmission of various diseases of plants and animals. The first one to be isolated in crystalline condition was the virus which causes the tobacco mosaic disease. When denatured or slightly modified by the action of reagents, the protein loses the power of inducing the disease. A study of the physical properties of the virus proteins indicates that the molecules are rod-shaped.

The name *filterable virus* was originally given to these disease-producing agents because they would pass through filters which would hold back even the smallest bacteria. Unlike bacteria and almost all infectious organisms, filterable viruses do not multiply apart from the living cells of the plant or animal they infect. The smaller virus proteins are of the same order of size as the largest nonvirus proteins known. For example, hemocyanin, the blue protein which contains

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copper and transports oxygen in the horseshoe crab, has a molecular weight of nearly 9,000,000; this corresponds to a spherical molecule of about 250Å diameter. The largest virus molecules studied, however, correspond to organisms which have been long recognized as living and which can multiply outside a living cell (diameter greater than 1500Å). Thus from the point of view of size and the ability to infect a large organism (the host), there is no sharp distinction between viruses and the smallest living organisms which transmit disease. Whether there is a sharp distinction in regard to complexity of structure and the methods of reproduction or growth is still undetermined.

QUESTIONS AND PROBLEMS

1. What are the three general classes into which the naturally occurring amino acids may be conveniently divided?

2. Write structural formulas for two representatives of each of the three classes of amino acids.

3. In what respects are the members of the three classes similar? In what respects different? (Consider physical properties and chemical reactions.)

4. Would you expect alanine to be more or less soluble in water solutions containing (*a*) glycine, (*b*) a tetrapeptide, (*c*) albumin? Why?

5. What methods are available for separating a mixture of glycine, phenylalanine, proline, and valine?

6. By what chemical reactions could you distinguish between a dilute aqueous solution of (*a*) egg albumin, (*b*) a partially hydrolyzed albumin, and (*c*) a mixture of the amino acids resulting from complete hydrolysis?

7. Outline two methods for preparing alpha amino acids.

8. How may polypeptides be synthesized?

9. A soluble protein which on hydrolysis yields a considerable amount of lysine, but no ammonia, evolves nitrogen when treated with a dilute solution of sodium nitrite and hydrochloric acid. What reaction do you think has taken place? What would you predict as to the binding capacity of the resulting protein for acid and base as compared with the original material?

10. How would you prepare hippuric acid in the laboratory? What would you predict concerning the behavior of this substance toward acids and bases?

11. The esters of the monoamino acids may be distilled under reduced pressure. Detail a procedure for separating the major constituent amino acids of silk fibroin from each other and the other amino acids formed in the hydrolysis of this protein.

12. By what steps in a process of degradation could you determine whether

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a certain tripeptide was leucyl-glycyl-valine or leucyl-valyl-glycine or valyl-leucyl-glycine? Devise procedures for synthesizing each of these tripeptides. Would you expect them to differ markedly in their physical properties or their behavior toward acids and bases?

13. Name three common substances of widely different properties which are proteins. What characteristics have they in common? What economic importance has each of these substances and on what properties does the economic importance of each depend?

14. If a water-insoluble protein yielded chiefly dibasic monoamino acids on hydrolysis, what would you predict in regard to its solubility in dilute acids and alkalies?

15. Outline the steps in three methods of preparing *d,l*-alanine. How would you resolve this amino acid?

16. Outline the steps in the synthesis of alanyl-glycyl-glycine from the component amino acids using the carbobenzyloxy method.

17. Outline a possible synthesis of tyrosyl cysteine using the benzyl group (introduced by the use of benzyl chloride) to protect OH and SH groups and the carbobenzyloxy group to protect the amino group.

18. Define the terms: *prosthetic group*, *enzyme*, *filterable virus*, *denaturation*, *iso-electric point*, *prolamine*, *protamine*, *conjugated protein*.

19. With the aid of structural formulas outline the course of the formation of urea from carbon dioxide and ammonia in the animal body.

20. Gelatine is a partially hydrolyzed fibrous protein prepared commercially from hides. How would you distinguish it from a gelatinous carbohydrate, agar-agar? How would you determine the amount of gelatine in a mixture of the two?

21. Compare and contrast the phenomena of: (*a*) cooking an egg, (*b*) destroying bacteria by sterilization, (*c*) inactivation of an enzyme by heating.

22. How do you account for the stability (resistance toward hydrolysis) of the C = NH in creatine and arginine? Arginine and histidine contain one relatively strong basic group. What is the explanation in each case?

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Chapter 20

CERTAIN BIOCHEMICAL PROCESSES

The Carbon and Nitrogen Cycles. Every student of chemistry knows that green plants absorb carbon dioxide from the atmosphere and, with the aid of the radiant energy of sunlight, convert this gas into a variety of complex substances. Simple nitrogen compounds from the soil supply the nitrogen for the building of proteins, and small amounts of other elements, such as phosphorus and sulfur, are also incorporated into the structure of the organic compounds produced in growing plants. The basic reaction in this process of photosynthesis is the hydrogenation (reduction) of carbon dioxide; the hydrogen atoms come from water molecules and oxygen gas is liberated; the reaction is strongly *endothermic*, the necessary energy being supplied by the sunlight.

BASIC REACTION OF PHOTOSYNTHESIS

$$CO_2 + \underset{\text{From water}}{2H} + \underset{\text{(About 100 kg-cal per mole)}}{\text{energy from light}} \longrightarrow \underset{\text{As complex compounds}}{\{CH_2O\}} + \tfrac{1}{2}O_2\text{(as gas)}$$

The possible mechanism of photosynthesis will be discussed later; while starch and cellulose correspond to the reduction of carbon dioxide to the *equivalent* of the empirical formula $\{CH_2O\}$, there is no evidence for the formation of formaldehyde. The fats and proteins represent a further hydrogenation (reduction).

When carbohydrates, fats, and proteins are oxidized in plants and animals by atmospheric oxygen through a series of reactions, energy is liberated. Thus there is in nature a cycle of carbon and nitrogen corresponding to a synthesis of complex substances with absorption of energy and their degradation with evolution of energy.

ENDOTHERMIC HYDROGENATION

$$\left.\begin{array}{l} CO_2 \\ H_2O \\ NH_4 \text{ salts} \\ \text{Inorganic salts} \end{array}\right\} \begin{array}{c} \xrightarrow{\qquad\qquad} \\ \text{100–150 kg-cal per mole of } CO_2 \\ \xleftarrow{\qquad\qquad} \end{array} \left\{\begin{array}{l} \text{Carbohydrates} \\ \text{Fats} \\ \text{Proteins} \qquad +O_2 \text{ (gas)} \\ \text{Other complex} \\ \text{organic compounds} \end{array}\right.$$

EXOTHERMIC OXIDATION

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It was formerly believed that the only way in which living organisms could obtain energy for this endothermic synthetic process was by absorbing light. We now know that this is not so. In plant and animal cells the fixation of carbon dioxide by hydrogenation (reduction) can take place without the absorption of light; the necessary energy may be supplied by oxidation reactions which are coupled with the reduction. Certain bacteria, for example, oxidize hydrogen sulfide to sulfur and sulfur to sulfuric acid; the energy thus liberated enables the bacterial cells to reduce carbon dioxide. In the over-all picture, however, the role of these microorganisms is insignificant. Much more important is the fact that *many living cells of plants and animals reduce carbon dioxide to carbohydrates even while carbohydrates or their degradation products are being oxidized to carbon dioxide.*

This remarkable fact has been established by using carbon dioxide in which the carbon atom was either a heavy or light isotope of the normal carbon of atomic weight 12. (Carbon with atomic weight 11, C^{11}, can be followed as it is radioactive; carbon of atomic weight 13, C^{13}, can be followed by the use of a mass spectrograph.) The isotopic carbon was found in the carbohydrate even when the living cells were evolving carbon dioxide. This shows that the carbon cycle written above represents a very general phenomenon probably characteristic of many, if not all, living cells.

We can no longer regard the synthesis of organic compounds from carbon dioxide as a reaction confined to green plants and a few bacteria. Nevertheless it is clear that only when the energy for the synthesis comes from some source other than the oxidation of organic compounds is there a real net gain in stored-up energy. Therefore, the significance of the *green plants as the primary source of organic compounds* is not altered by the new findings. The bacteria which oxidize inorganic substances are of very minor importance. We may still say that the green plants store up the energy of sunlight to the extent of some 100 to 150 kg-cal per mole of carbon dioxide, and the subsequent oxidation reactions in the plant or animal cells release this energy. The radiant energy from the sun is therefore the basis of all life. Where the organic matter has been preserved through geologic ages as coal, oil, or natural gas, the same energy is available to us today (p. 103).

Metabolism. The chemical reactions which occur in living cells are often referred to as metabolic changes or *metabolism*. Sometimes the words *anabolism* and *catabolism* are used to designate the building

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up and the breaking down of complex molecules respectively. When the building-up process starts with carbon dioxide and uses light energy, we speak of *photosynthesis;* when the energy is supplied by other reactions the process is often referred to as *chemosynthesis.* This latter term may also be used when other substances than carbon dioxide are the primary factors.

A great variety of metabolic changes are going on all the time in living cells. For the most part we observe only the *net* change with respect to those substances which disappear and those which appear outside the cells. The two gases, oxygen and carbon dioxide, are obviously of prime importance and by measuring the absorption and evolution of these gases by an organism or by a group of cells one can learn a good deal about the net changes which are taking place. For example, if photosynthesis is taking place rapidly, carbon dioxide disappears and oxygen appears rapidly. Conversely, if oxidation is taking place rapidly and is not offset by a chemosynthetic process involving carbon dioxide, oxygen is absorbed and carbon dioxide is evolved. The rate of evolution and absorption of these gases is a measure of the rate of chemical activity within the cells and is sometimes referred to as the *metabolic rate.* The rate at which energy is liberated or absorbed in photosynthesis is closely related to the metabolic rate.

In a simple organism, a great variety of catabolic and anabolic reactions must occur within a single cell; this is true of the green algae, for example, which grow on inorganic aqueous media and carbon dioxide by a photosynthetic process. It is also true of yeasts and molds and bacteria which obtain their energy by oxidizing the organic materials (usually carbohydrates and proteins) on which they live by means of atmospheric oxygen (aerobic conditions) to carbon dioxide. In the absence of oxygen (anaerobic conditions) these colorless organisms obtain energy by converting their nutrient materials into products other than carbon dioxide; for example, lactic acid or ethyl alcohol may be formed. These anaerobic catabolic processes are often referred to as *fermentation.* We shall study a few in detail later in this chapter.

In the higher plants and animals there is a differentiation in functions of the various groups of cells. While probably all living cells are able to provide energy for themselves, they may perform different chemical reactions of significance for the organism of which they are a part. Therefore, the study of the separate parts of the higher plants

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and animals enables the biochemist to isolate certain biochemical processes. The techniques for doing this cannot be considered in this book, but we shall give the results of a few such investigations. The biochemist may also study biochemical processes by means of extracts of living cells which contain the biochemical catalysts, *the enzymes*, some of which can now be prepared in a pure state. Experiments with extracts, enzymes, or tissues are referred to as *in vitro* experiments; experiments with living plants or animals are called *in vivo* experiments. The evidence from the former, while of the greatest value, must be checked by the latter type of experiment in order to ascertain with a high degree of certainty what actually goes on in living cells.

The Metabolic Pool. Very interesting evidence about the nature of the chemical transformations which go on in living tissue has been obtained by studying the higher animals. Not long ago it was thought that the body of a full-grown animal was nearly static, the organic compounds of which it was composed changed only slowly. If this were true, then the primary function of the foodstuffs would be to supply energy to keep the temperature of the body constant (in warm-blooded animals) and for mechanical energy (muscular work). The analogy with a combustion engine was sometimes stated. This point of view has been shown to be erroneous by feeding experiments in which organic compounds containing isotopic carbon, nitrogen, and hydrogen atoms were used. The "tagging" of certain of the atoms enabled the biochemist to trace their fate in the animal body. (A similar "tagging" of the carbon atom in carbon dioxide established the simple but surprising fact, referred to above, that many colorless plant and animal cells can reduce this gas.) Instead of the "tagged" atoms appearing primarily in the excreta or the products of combustion, they were found widely distributed throughout the body, and the distribution took place very rapidly.

One or two examples will illustrate the new discoveries. Fatty acids were prepared in which some of the hydrogen atoms of the chain were replaced by heavy hydrogen (deuterium, at. wt 2). These acids were fed to grown rats otherwise living on a normal diet and after a period the rats were killed. The body tissues were analyzed and the amount of heavy hydrogen in the materials from different organs was determined. In the first place, it was clear that the acids containing the heavy hydrogen atoms were rapidly distributed throughout the body. This fact shows that the structure of an organism is continually under-

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going change. In the second place, while the largest portion of the heavy hydrogen was found in the particular acid fed, it was also found in fatty acids with longer and shorter chains and in a complex cyclic compound associated with fats (cholesterol, p. 585). Experiments with amino acids in which heavy nitrogen (N^{15}) was present gave similar results. The isotopic nitrogen (N^{15}) was found to be widely distributed in the proteins of the body in a short time and in a great many (but not all) amino acids, though it was only introduced in one amino acid.

Many experiments of this sort have led to the conclusion that, even in a higher organism with clearly differentiated functions for different organs, the body seems to be perpetually in a state of flux. The appearance of stability is in a sense an illusion for it is only a *net* change which we ordinarily measure when we study foods, excreta, and tissue. It would appear that there is a sort of "metabolic pool" of relatively simple molecules in an organism from which the different types of cells keep reconstructing their components. Probably the fatty acids are broken down into substances containing two or three carbon atoms; the amino acids are almost certainly transformed into ketonic acids and ammonia (p. 358); carbon dioxide itself (largely present as the bicarbonate ion in the body fluids) must be considered as part of this metabolic pool.

That the process of breakdown or degradation is not always complete is shown by the fact that usually the fatty acid or the amino acid which contained the tagged atom (or atoms) predominates as such in the body. Thus, while deuterium is found distributed among all the fatty acids when added as deuteropalmitic acid, nevertheless the major part of it turns up as deuteropalmitic acid. Therefore, molecules as complex as this can find their place in the structure of an organism into which they are introduced without first being degraded to smaller units and then rebuilt.

A candle flame is perhaps the nearest analogy we have in nonliving phenomena to a living organism. The flame appears to have a constant form or structure, but we know that it merely represents a balance between the fuel gases coming in and the products of combustion going out. The energy of the combustion heats the particles of carbon (product of the cracking of the fuel) to a glowing temperature. The candle itself is a mixture of complex compounds. To study the detailed reactions of the candle flame would seem nearly a hopeless undertaking, though to study the over-all net effect is not hard at all.

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The biochemist is faced with a not dissimilar situation if the candle flame be the analog not of a higher organism but a single cell. He has been aided by the fact that cells differ a great deal in the predominant chemical reactions which take place within them; he has also been assisted by his ability to extract the catalysts involved in many processes. As a result we know a great deal about certain biochemical transformations, particularly the degradation of carbohydrates and their chemosynthesis. We know much less about their photosynthesis and almost nothing about the synthesis of proteins, though we have learned something about protein catabolism. Before considering a few special processes, some general considerations may not be out of place.

General Characteristics of Biochemical Processes. Water is a necessary condition for life. All biochemical processes take place either in dilute aqueous solution or at or near the interface of such solutions with fatty or fibrous layers. The preservation of plant and animal material by desiccation depends on the fact that in the absence of water the enzymes which are initially present and would cause decomposition cannot act. For the same reason, bacteria, molds, and fungi cannot grow on dried material. With few exceptions, the aqueous fluids in plants and animals and the aqueous media on which organisms grow are nearly neutral. In the higher organisms the presence of salts of weak acids (particularly the phosphates) keeps the solutions at the proper acidity. In addition the presence of other salts keeps the osmotic pressure of the body fluids at the proper value.

Biochemical reactions take place at an appreciable rate only in the presence of specific catalysts which are called *enzymes*. These enzymes are proteins and a number of them have been isolated in a pure crystalline condition. Like most reactions, these catalyzed biochemical transformations are accelerated by rise in temperature (about twofold per 10°). At temperatures of 0° and below a vast majority of them take place very slowly. On this fact depends the common practice of preserving foods by refrigeration.

Since the enzymes are proteins they can be denatured (p. 370) by heat or certain reagents. When they are denatured they are no longer active. In most common organisms, the enzymes are rendered inactive by heating for a short time above the boiling point of water. This is the basis for pasteurizing milk and sterilizing by heat; the denaturation of the proteins by heat destroys the enzymes and hence "kills" the bacteria in which they play literally the vital role. The preserva-

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tion of plant and animal tissues in alcohol or with formaldehyde (present in embalming fluid) depends likewise on the denaturation of the enzymes. Preservation of material by small amounts of specific preservatives or antiseptics such as phenol (carbolic acid), salicylic acid, and similar substances is probably another story. Here we are dealing with special interactions between microorganisms and organic compounds. How specific this interaction may be is shown by the fact that some compounds which are nontoxic to higher organisms are very toxic to the microorganisms which cause disease (Chap. 32).

Enzymes. That extracts of living cells contain substances which bring about certain chemical reactions has been known for many years. These naturally occurring catalysts were also known to be sensitive to heat and to the action of chemical reagents. By evaporating the extracts from certain plant and animal cells under diminished pressure at room temperature, amorphous powders were obtained which had high catalytic activity. But such powders were still very impure and contained large quantities of inert organic and inorganic material.

A great step forward was made in the study of enzymes when it was found that certain crystalline proteins could be isolated which had high enzymatic activity. They retained this activity as the purification by crystallization proceeded. More than a dozen enzymes have now been prepared in the crystalline condition. They include urease (p. 330), several protein-splitting enzymes such as pepsin, and several enzymes required in the oxidation of carbohydrates. Like all proteins these substances are easily altered or denatured. When this occurs the enzymatic activity disappears. In a few instances this loss of activity can be restored by the same procedure used in reversing the denaturation of proteins. More often the change is irreversible. Enzymes usually lose their activity not only when heated, but also when treated with such powerful reagents as strong acids or strong alkalies or oxidizing agents. All these facts, taken together with what is known of the enzymes which have been crystallized, demonstrate that enzymes are proteins.

Enzymes are specific in their action. It will be recalled, for example, that emulsin will bring about the hydrolysis of beta glucosides but not of alpha, while maltase acts in just the reverse manner (p. 295). The catalytic activity of each enzyme is usually at a maximum at some temperature not greatly above room temperature and at a certain acidity. This maximum is the result of the operation of two conflicting

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tendencies: raising the temperature increases the rate of the reaction, but it also increases the rate of denaturation of the enzyme. The concentration of the material which is undergoing the chemical change (the substrate) is also often important. In certain processes, the accumulation of the products of the reaction slows down the enzymatic reaction. Coenzymes (or coferments) are relatively thermostable substances which are essential for the enzymatic action. Thus, calcium (in the ionic form) is a coenzyme for the clotting of milk by the enzyme rennin (conversion of the soluble protein caseinogen to the insoluble casein). We do not know why the calcium ions are necessary.

It has been often stated that the enzyme and substrate are related as a key to a lock. One can imagine that certain specific linkages must be present in both enzyme and substrate in order to allow the two substances to interact. Whether the interaction involves the formation of a chemical compound or is in the nature of adsorption is still an open question. Why the substrate undergoes chemical change after combination with or adsorption on the enzyme is far from clear. But there is nothing more mysterious about the nature of enzymatic action than about the action of catalysts in general. In a few instances, of which certain oxidizing enzymes are the best examples, the enzyme contains a prosthetic group and the function of this group can be understood: the protein may be thought of as a carrier, but one essential for the action of the enzyme. These prosthetic groups are also often referred to as *coenzymes*. The enzyme which decomposes hydrogen peroxide (catalase) and several oxidizing enzymes have definite prosthetic groups.

Classification of Enzymes. Enzymes are often classified according to the chemical transformation they bring about. On this basis we may separate the enzymes which bring about hydrolysis from those which are involved in oxidation and reduction. Of the former we recognize the following special types.

SOME CLASSES OF HYDROLYZING ENZYMES

1. Esterases, which hydrolyze esters.
   a. Lipases which hydrolyze fats.
   b. Phosphatases which hydrolyze esters of phosphoric acid.
   c. Other esterases.
2. Proteinases which hydrolyze proteins.
3. Peptidases which hydrolyze peptides.
4. Urease which hydrolyzes urea.
5. Deaminases which remove amino groups by hydrolysis.

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6. Carbohydrases.
   a. Amylases which hydrolyze starch and glycogen.
   b. Glycosidases which hydrolyze glycosides.

Closely related to the hydrolyzing enzymes are those enzymes (phosphorylases) which cause the transfer of a phosphate group from one compound to another in the course of carbohydrate metabolism, and those which bring about the cleavage of a complex carbohydrate by the introduction of a phosphate group. *Hexokinase* is the one example of the latter group. The enzyme which greatly accelerates the liberation of carbon dioxide gas from an aqueous solution of carbon dioxide is known as *carbonic anhydrase*. *Carboxylase* catalyzes the liberation of carbon dioxide from pyruvic acid. All three of these enzymes have been obtained in pure crystalline condition.

The **oxidizing and reducing enzymes** may be subdivided into those which contain a metallic atom and those which contain a prosthetic group which can add or lose two hydrogen atoms. Of the former, *peroxidase* which accelerates the decomposition of peroxides, *catalase* which acts in a similar fashion on hydrogen peroxide, and *cytochrome* all contain iron. Cytochrome which is distantly related to hemoglobin (p. 624) is involved in one of the steps in the oxidation of carbohydrates. Certain other oxidizing enzymes contain a copper atom. *Lactic dehydrogenase* and *flavoprotein* (an enzyme involved in respiration) are examples of oxidizing enzymes containing a strictly organic prosthetic group.

Among the enzymes which have been obtained in pure crystalline condition are urease, pepsin (a peptidase), trypsin (a proteinase), catalase, lactic dehydrogenase, flavoprotein, hexokinase, carboxylase, and carbonic anhydrase.

Equilibria and Rates in Biochemical Reactions. Catalysts, it will be recalled, change the rate of a reaction but do not alter the position of an equilibrium. Since in a living cell a continuous and rapid metabolic process is going on, we are concerned primarily with rates of *competing* chemical reactions. Furthermore, biochemical reactions as a rule liberate or absorb relatively small amounts of energy; a balanced or nearly balanced equilibrium is often at hand. It seems that living cells operate with reversible reactions where possible and can utilize or absorb energy in only small increments. Thus in the oxidation of carbohydrates we shall see that a complex series of changes take place so that at no one step is anything like 100 or so kg-cal of energy liberated, which would result if all at once one carbon

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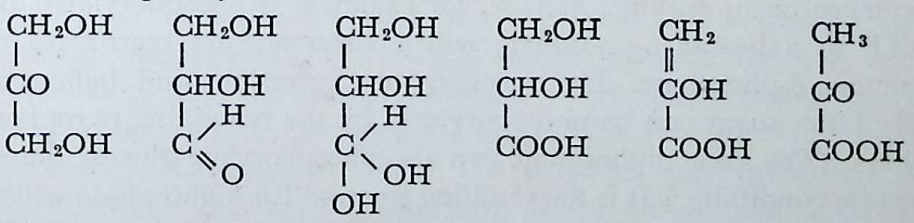
atom of a carbohydrate were oxidized by air to carbon dioxide. Apparently this necessity for reversible reactions with relatively small energy changes is a characteristic of biochemical transformations.

THE METABOLISM OF CARBOHYDRATES

The study of the metabolism of carbohydrates has been most exhaustive with a relatively few types of cells. Yeast, muscle tissue, and liver have received a great deal of attention; in addition the changes brought about by certain microorganisms which convert sugars into alcohols and acids have been studied. The whole subject is still in a state of exploration, and, while much knowledge has been accumulated, the full details of the changes which carbohydrates undergo in all variety of cells are far from known.

Formal Relationships. Before considering the details of carbohydrate catabolism in yeast and certain animal cells, the over-all structural relationship of certain compounds must be understood. Glyceric aldehyde and dihydroxyacetone are two trioses closely related to glucose and, as a first approximation, we may say that under enzymatic conditions these sugars are in equilibrium with glucose and with each other. (The energy changes are slight.) The dehydrogenation (oxidation) of the hydrate of glyceric aldehyde yields glyceric acid. (This can be brought about in the laboratory by the usual reagents.) Glyceric acid on dehydration should yield the enolic form of pyruvic acid which, under ordinary conditions, would isomerize almost completely to the ketonic form.



The Role of Phosphate. Apparently in the changes from glucose to three-carbon sugars and acids in the living cell the phosphate ion, $HOPO_3^{=}$, plays a very important role. (Since the reactions involved occur at or near the neutral point, phosphoric acid is present largely as this ion.) The active compounds involved in the actual biochemical changes are esters of this ion. They are usually not formed by direct interaction but are the result of the phosphorylating agent which occurs widely distributed in nature, adenylic acid pyrophosphate,

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also known as *adenosine triphosphate*. This is a complex compound and we need be concerned for the present only with the triphosphate portion. (Adenylic acid pyrophosphate contains a nitrogenous ring compound, adenine, a pentose, ribose, and three phosphate groups. See p 621.) We shall represent the substance by the following abbreviated formula, $AO\overset{\overset{OH}{|}}{P}-O-\overset{\overset{OH}{|}}{P}O_3^{=}$ and refer to it as ATP; the corresponding diphosphate and monophosphate will be referred to as ADP and AMP (adenylic acid). ATP and ADP contain the pyrophosphate linkage and can be regarded as the equivalent of an acid anhydride, for a pyrophosphate is analogous to acetic anhydride in that both react with water in a fairly strongly exothermic reaction.

$$(CH_3CO)_2O + H_2O \longrightarrow 2CH_3COOH + 14 \text{ kg-cal}$$

$$\underset{\text{(Ion of pyrophosphoric acid)}}{(PO_3^{=})_2O} + H_2O \longrightarrow 2HOPO_3^{=} + 10 \text{ kg-cal}$$

Because the reaction between a pyrophosphate and water is exothermic by some 10 kg-cal, the biochemist speaks of the pyrophosphate link as *energy rich*. The significance of this will be clear later.

Just as acetic anhydride is an acetylating agent, so pyrophosphates under certain circumstances are phosphorylating agents. In the presence of an enzyme, glucose, for example, is phosphorylated by ATP to a hexose 6-phosphate which enzymatically rearranges to fructose 6-phosphate. The reactions are reversible and balanced. The latter sugar can be phosphorylated by the remaining pyrophosphate. (The same diphosphate can also phosphorylate glucose under certain conditions.) It is the resulting fructose 1,6-diphosphate which reversibly decomposes into two phosphorylated triose molecules in the presence of an enzyme. These two trioses are again in equilibrium with each other. (It will be recalled that the energy changes in the aldol condensation are slight and the reaction is often in equilibrium.) We may sum up therefore as follows:

$$\text{Glucose} + \text{ATP} \overset{\text{Enzyme}}{\rightleftharpoons} \text{Glucose 6-phosphate} + \text{ADP}$$

$$\text{Glucose 6-phosphate} \underset{\text{Enzyme}}{\rightleftharpoons} \text{Fructose 6-phosphate}$$

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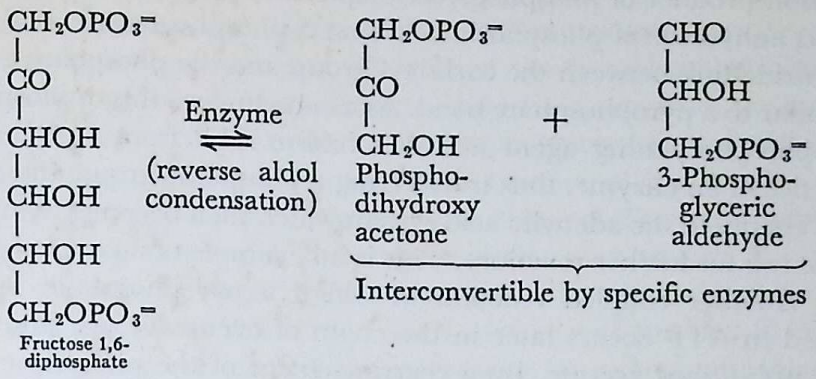
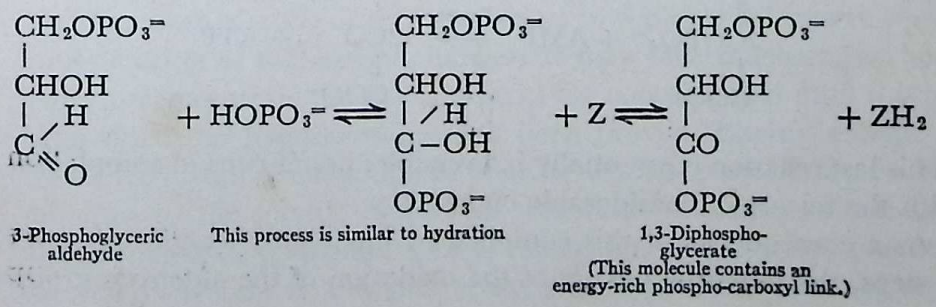
$$\text{Fructose 6-phosphate} + \text{ADP} \overset{\text{Enzyme}}{\rightleftharpoons} \text{Fructose 1,6-diphosphate} + \text{AMP}$$



Formation of Pyruvate. Pyruvic acid (the pyruvate ion) seems to be the key substance in the breakdown of carbohydrates, at least in those cells which have been so far thoroughly studied. Its empirical formula, $C_3H_4O_3$, represents a dehydrogenation (oxidation) of glyceric aldehyde, $C_3H_6O_3$. If pyruvate were formed by the direct oxidation of glyceric aldehyde by oxygen, considerable heat (about 25 kg-cal) would be evolved; corresponding to this large energy release, the reaction would run to completion. Actually the process is far more complicated. In the first place, instead of a hydrate of the aldehyde being an intermediary as in so many oxidations of aldehydes (p. 129), an addition product with the inorganic phosphate ion, $HOPO_3^{=}$, is involved. In the second place, the hydrogen is transferred from the addition product not to gaseous oxygen directly, but to an enzyme which in turn reduces another enzyme, and only after several steps does the oxygen molecule receive the hydrogen atoms.

Let us concentrate our attention on the first step and leave aside the series of oxidizing enzymes. The reactions may be written as follows, where Z is the oxidized form of the enzyme and ZH_2 the reduced form.



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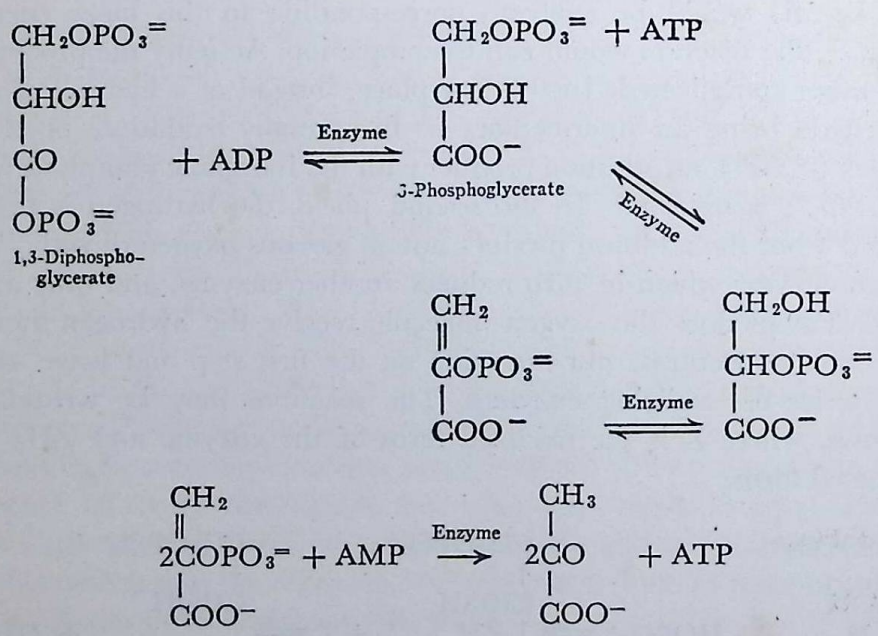
The 1,3-diphosphoglycerate formed by the dehydrogenation of the addition product of phosphoglyceric aldehyde may be regarded as a mixed anhydride of phosphoric acid and 3-phosphoglyceric acid; the anhydride link between the carboxyl group and the phosphate group is similar to a pyrophosphate bond. As a consequence this diphosphate is a phosphorylating agent and can reform ATP from ADP in the presence of an enzyme, thus transferring a phosphate group and some of its energy to the adenylic acid system which then becomes available to the cell for further reactions. This is an example of a coupled reaction. Another coupled reaction in which a pyrophosphate link is formed in ATP occurs later in the chain of events we are studying. The 3-phosphoglycerate, by a rearrangement of the phospho group and loss of water, becomes a phosphopyruvate. In this compound the enol-phosphate link is also energy rich (it is in a sense a mixed anhydride for the enolic forms are acids); and the energy which would be liberated as heat if this compound hydrolyzed to phosphoric acid and pyruvic acid (ketonic form) can be used to place *two* phosphoric acid groups on the adenylic acid system. The reactions are as follows:



(This last reaction is essentially irreversible; i.e., it runs to completion with the release of considerable energy.)

As a consequence of this complicated but highly significant series of steps, the potential energy of the oxidation of the aldehyde group

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of the triose to an acid and the dehydration and rearrangement of a dihydroxy compound is transferred to pyrophosphate linkages of adenosine triphosphate. This substance is then ready to start the cycle over again, but the *net* result is a gain of one pyrophosphate link or about 10 kg-cal of stored-up energy. This gain comes from the formation of ATP from AMP by the 1,3-diphosphoglycerate as explained in the preceding paragraph. For the transformation of 1 mole of glucose the gain of pyrophosphate links is two, or 20 kg-cal of stored-up energy.

The hydrogen atoms of the enzyme represented as ZH_2 are eventually oxidized to water by the oxygen of the air through several stages; in no one of these is more than a fraction of the heat liberated that would have resulted if the interaction of oxygen and glyceric aldehyde had occurred all at once. *Thus, we see that a whole series of reversible steps has broken down the heat evolution into small amounts and has allowed a certain amount of energy to be stored in pyrophosphate linkages.*

Coupled Reactions. Coupled reactions are of the greatest importance in biochemistry. A very simple example of a coupled reaction was met early in this book in considering one of the industrial methods of preparing acetic anhydride (p. 165). In this process, the oxidation of acetaldehyde by oxygen, a strongly exothermic reaction was coupled with the dehydration of acetic acid to acetic anhydride (endothermic by about 15 kg-cal). As a consequence the over-all reaction, acetaldehyde + oxygen $\longrightarrow$ acetic anhydride + water, was exothermic and proceeded to completion. There is a striking analogy between this reaction and those just mentioned in which the oxidation of an aldehyde group is coupled with the formation of pyrophosphate (essentially an anhydride). But it is important to note that the way the two sets of reactions are coupled is very different; in the biological reaction the oxidation does not involve molecular oxygen but does involve a special addition product of the aldehyde; in the industrial reaction a peroxide is an intermediary.

Very often the biochemist suspects that two reactions are coupled together from a study of the *net* changes in a biological system plus a consideration of the energy changes. It may take much study, however, to demonstrate the mechanism of the coupling and until this has been done the hypothesis has not been proved. Energy cannot be transferred from one reaction to another without a mechanism which amounts to the joining of the two reactions into one, as the cases already cited demonstrate. This is the reason why coupled reactions are relatively rare in the laboratory or industry; one can not bring

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about an endothermic reaction by putting in a flask the components and two other substances which will react exothermically. (If this were possible as a general proposition, organic chemistry would be a vastly different subject!) On the other hand, biological processes often involve the coupling together of two or more reactions. Apparently, specific enzymes have been developed in nature which bring about many of the usual types of chemical reactions by special steps so that the mechanisms of two reactions can become geared together. In this way living organisms can use the energy of exothermic reactions to bring about other reactions which in the laboratory will not take place because of grossly unfavorable equilibria.

Glycolysis in the Muscle. In the absence of oxygen, glycogen (p. 300), the reserve carbohydrate of the animal body, is broken down into lactic acid (as lactate). Energy is liberated both in the form of heat and mechanical work. This is a rapid process and the possibility of such a quick utilization of some of the potential energy of glycogen makes possible the action of muscle tissue. For recovery, oxygen is required to oxidize the lactic acid; during this oxidation a certain amount of glycogen is reformed by a chemosynthesis (the result of a series of coupled reactions in which the energy of oxidation provides the energy for resynthesis).

Considering first the anaerobic breakdown of glycogen, we find that the process of pyruvate formation already considered is basic. The glucose 6-phosphate is formed by the splitting of the glycogen molecule by the $HOPO_3^-$ ion in the presence of an enzyme. The reaction is reversible and analogous to hydrolysis.

$$\underset{\text{Glycogen}}{(C_6H_{10}O_5)_x} + xHOPO_3^- \overset{\text{Enzyme}}{\rightleftharpoons} x \text{ Glucose 6-phosphate}$$

The formation of pyruvate then proceeds as outlined in the preceding section, but the hydrogen atoms of the enzyme, ZH_2, are transferred not to gaseous oxygen but to a molecule of pyruvate to yield lactate.

$$CH_3COCOOH + ZH_2 \rightleftharpoons CH_3CHOHCOOH + Z$$

It will be seen that the over-all stoichiometric equation is such that only glucose and lactic acid appear; from the heats of combustion we can estimate that the reaction is exothermic by about 15 kg-cal.

$$\underset{\text{Glucose}}{C_6H_{12}O_6} \longrightarrow \underset{\text{(i.e., } C_3H_6O_3)}{2CH_3CHOHCOOH} + \text{approx. 15 kg-cal (reactants and products in aqueous solution)}$$

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In addition we should add the heat of neutralization of two molecules of lactic acid as, under the neutral condition of the muscle tissue, the product is the lactate ion. This additional heat is about 22 to 25 kg-cal per mole of glucose. Of the about 40 kg-cal of energy thus available, some 20 kg-cal can be stored as two pyrophosphate linkages as we have seen. For the only difference between the formation of pyruvate and lactate is the fate of the hydrogen atoms.

It is this stored energy in the pyrophosphate links of ATP which is available for muscular work. The protein of the muscle fibers apparently can be rapidly phosphorylated by ATP and in so doing contraction of the muscle takes place together with the liberation of heat. Thus some of the stored up energy in glycogen is made available for rapid mechanical work (muscular action) when the organism so desires.

Alcoholic Fermentation. The fermentation of sugar to alcohol by yeast is not only a very ancient art but a biochemical reaction which in recent years has been exhaustively studied. Indeed, one of the earliest observations about enzyme action was the demonstration that aqueous extracts of crushed yeast could also bring about the conversion of glucose to alcohol. This showed that the biochemical catalyst could in some instances, at least, be separated from the living cells without damage.

As a result of many *in vitro* and *in vivo* experiments it has been established quite conclusively that *in the absence of oxygen* the yeast cells transform glucose to ethyl alcohol as follows: Glucose through the series of reactions involving phosphate is broken down to pyruvic acid. The yeast cell contains an enzyme (not found in animal tissue) which catalyzes the decarboxylation of pyruvic acid to acetaldehyde. This aldehyde in turn is the acceptor of the hydrogen atoms removed by the enzyme in the course of the formation of pyruvic acid. Thus alcoholic fermentation differs from glycolysis only in that acetaldehyde is reduced to ethyl alcohol rather than pyruvic acid to lactic acid. Reactions of alcoholic fermentation:

$$\underset{\text{Glucose}}{C_6H_{12}O_6} \xrightarrow[\text{and specific enzymes}]{\text{Through several steps involving phosphate}} CH_3COCOOH + ZH_2 \text{ (reduced enzymes)}$$

$$CH_3COCOOH \xrightarrow{\text{Enzyme}} CH_3CHO + CO_2$$

$$CH_3CHO + ZH_2 \xrightarrow{\text{Enzyme}} CH_3CH_2OH + Z \text{ (returns to cycle)}$$

Some of the first studies of alcoholic fermentation of glucose by cell-free yeast juice

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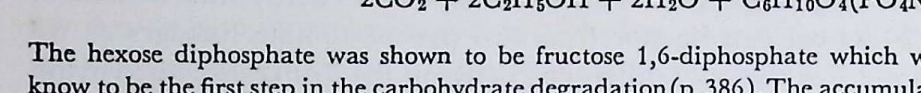
showed that inorganic phosphate was consumed in the reaction and a hexose diphosphate was formed as well as carbon dioxide and alcohol. The over-all reaction was:



$$2C_6H_{12}O_6 + 2Na_2HPO_4 \longrightarrow 2CO_2 + 2C_2H_5OH + 2H_2O + C_6H_{10}O_4(PO_4Na_2)_2$$

The hexose diphosphate was shown to be fructose 1,6-diphosphate which we now know to be the first step in the carbohydrate degradation (p. 386). The accumulation of this ester in the cell-free fermentation of glucose (*in vitro*) represents the fixation of two phosphate groups on a hexose per molecule of glucose converted to alcohol and carbon dioxide. The explanation is now clear. The *net* gain of two pyrophosphate links in ATP as a result of the transformation of 1 mole of glucose to 2 moles of pyruvic acid (p. 389) causes the ATP to phosphorylate 1 mole of hexose twice under the conditions of alcohol production (artificial conditions of cell-free extract). Thus, the phosphate groups which in glycolysis in animal tissue are stored up as ATP ready for muscular transformation are transferred to another glucose molecule in fermentation and the energy is liberated as heat.

Oxidation of Pyruvic Acid. The student will observe that in spite of a long and complicated series of reactions we have so far accounted only for the oxidation of four hydrogen atoms per mole of glucose (two per mole of triose). How do plant and animal cells bring about the combination of oxygen gas and the other eight atoms of hydrogen and the six carbon atoms? This over-all complete oxidation of glucose, of course, is a reaction of fundamental significance. Yet we are still uncertain as to many of the stages. Indeed, it is probable that in different cells different routes may be followed. Probably in most cells, however, pyruvic acid is formed as already indicated, and pyruvic acid is then transformed into carbon dioxide and water by several series of steps. These seem to involve the formation of dibasic and tribasic ketonic acids by condensation reactions, and then loss of carbon dioxide from the beta ketonic acids. While the steps at first sight may seem to be without rhyme or reason, we must recall that, in general, biochemical processes occur with small release of energy and they are essentially reversible. It is not easy to write hypothetical reactions by which pyruvic acid could be oxidized completely in steps which fulfill these conditions, unless more complex molecules are first formed. We may say that this explains why such a complicated mechanism seems to be required.

Before outlining the probable course of events, the interrelation of oxidation and fermentation should be emphasized. In the presence of plenty of oxygen living cells oxidize pyruvic acid rapidly, and the

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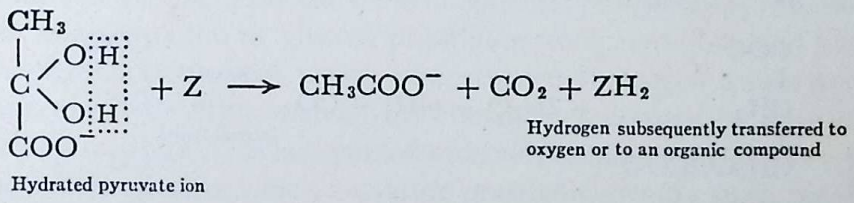
complete oxidation of glucose is therefore the predominant reaction. In the absence of air (anaerobic conditions), pyruvic acid accumulates and may undergo other transformations, as for example, to lactic acid (glycolysis) or ethyl alcohol (fermentation). The production of lactic acid can also be brought about by the enzyme system in certain bacteria under anaerobic conditions (lactic acid fermentation) and this is one commercial source of lactic acid. Thus, fermentations are usually transformations of glucose to simpler chemical substances in the living cell with the release of energy. Years ago, Pasteur recognized the connection between fermentation and oxidation and summed it up by saying "Fermentation is life without oxygen." With certain qualifications this statement can stand today.

The Oxidation of Acetate Ion. One way of looking at the complicated oxidation of pyruvic acid in living cells is to center attention on acetic acid or, really, the acetate ion. Pyruvate is converted into acetate and carbon dioxide by a number of different routes and enzyme systems; two hydrogen atoms are transferred to oxygen or some other molecule in the process. Probably the hydrated ion is actually the reactant.



Two more hydrogen atoms and one carbon atom per triose (four hydrogen atoms and two carbon atoms per hexose) have thus been taken care of, but the real problem the organism is confronted with is the disposal of the acetate ion. Apparently to accomplish this, ketonic acids must be built up by synthesis and then oxidized. The ion of oxalacetic acid can be regarded as a cycling substance with which acetate condenses to form a tribasic hydroxy acid which is then oxidized in steps back to oxalacetate, carbon dioxide, and water. (Phosphate enters the molecule in several of the reactions and specific enzymes are involved.) The following is a simplified account of one path of the oxidation of pyruvic acid.

1. Formation of acetate.

$$CH_3COCOO^- + H_2O \longrightarrow CH_3COO^- + CO_2 + 2[H]$$

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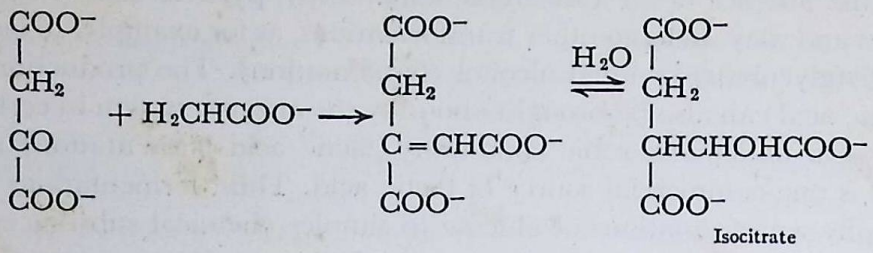
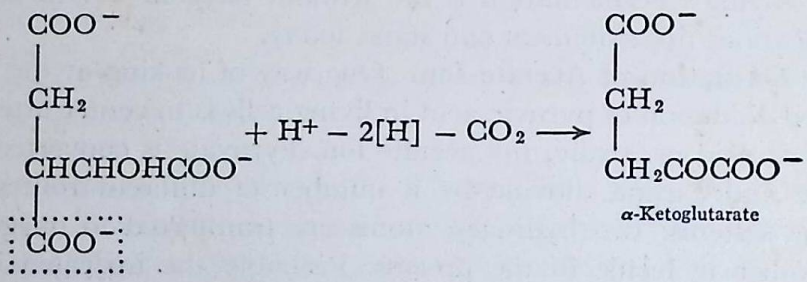
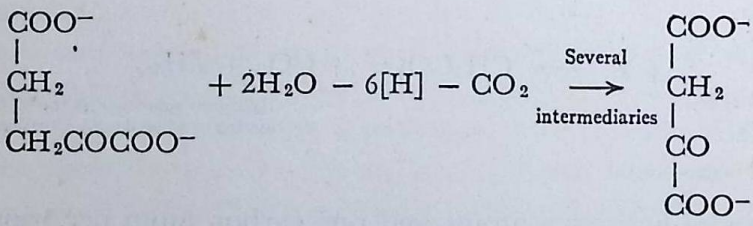
2. Condensation of acetate with oxalacetate.



3. Oxidation to α-ketoglutaric acid.



4. Regeneration of oxalacetate.



It will be seen that, in this process of oxidation of pyruvic acid, two hydrogen atoms are removed and 1 mole of carbon dioxide liberated in the first step; in the second step, no oxidation is accomplished, but in the third step, two hydrogen atoms are oxidized and one more mole of carbon dioxide is formed; while in the fourth step (which is a series of reactions) the remaining carbon atom is completely oxidized and six hydrogen atoms are removed. The sum total is therefore:

$$CH_3COCOO^- + H^+ + 3H_2O \longrightarrow 3CO_2 + 10[H]$$ (which eventually goes to H_2O with oxygen from the air)

A further analysis of the fourth step of this process is of importance for the biochemist for it reveals that succinic acid, fumaric acid, and malic acid (as their ions) are involved. The reactions are all reversible in the presence of suitable enzymes.

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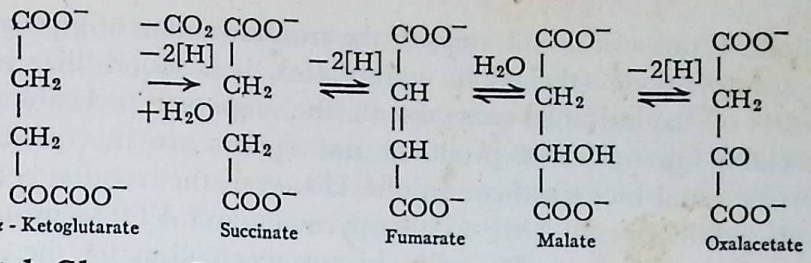

Total Glucose Catabolism. We may attempt to sum up the anaerobic and aerobic catabolism of glucose by the following simplified diagram which gives the over-all picture.

$$\text{Glucose} + \text{AMP} + 2\text{HOPO}_3^{=} \longrightarrow 2\ \text{Pyruvate} + 4[\text{H}] + \text{ATP}\ \text{(energy stored)}$$

$$2\ \text{Pyruvate} + 4[\text{H}] \xrightarrow{\text{Anaerobic}} 2\ \text{Lactate}$$

$$2\ \text{Pyruvate} + 4[\text{H}] + 6\text{O}_2 \xrightarrow[\text{Many steps and enzymes}]{\text{Aerobic}} 6\text{CO}_2 + 6\text{H}_2\text{O}$$

Several of the many enzymes which are involved in the catabolism of glucose have been obtained in pure, crystalline form. It is therefore possible to study with relative certainty and ease the processes which they catalyze. These enzymes include *hexokinase*, responsible for the formation of glucose 6-phosphate from glucose; *phosphorylase*, responsible for the formation of glucose phosphate from glycogen; and *lactic dehydrogenase*, the enzyme which removes two hydrogen atoms from glyceric aldehyde diphosphate (the enzyme represented by Z in the preceding section). This last-named enzyme is an example of the type already referred to in which a definite prosthetic group can be identified. This prosthetic group is known as *cozymase*, or *coenzyme I*, or *codehydrogenase;* it is of relatively low molecular weight and its structure has been determined with certainty (p. 623). This coenzyme or prosthetic group can add or lose two hydrogen atoms reversibly (i.e., it is a hydrogen acceptor) and thus enters into the reactions it catalyzes in a more definite way than do the hydrolyzing enzymes. The coenzyme is found linked to various large protein molecules which are necessary for its action and which give the enzyme specificity with regard to the particular hydrogenation and dehydrogenation reaction into which it enters.

Synthesis of Glycogen. In muscular tissue and in the liver in the presence of oxygen, lactic acid disappears and glycogen is formed. This is a reversal of the glycolysis already described in detail. The energy necessary for this reconversion is supplied by the oxidation of lactic acid which is thus in some way coupled with the resynthesis

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reactions. If one studies the steps in the transformation of glycogen to 2-phosphopyruvate (the enolic phosphate), it is found that in the presence of the suitable enzymes all the steps are reversible; i.e., appreciable quantities of products and factors are in equilibrium under the usual biological conditions. However, the reaction between phosphopyruvate and AMP to give pyruvate and ATP seems to run to essential completion. Therefore in any mechanism for the resynthesis of glycogen by the route of its degradation, the formation of 2-phosphopyruvate seems to be the stumbling block. Once this is formed from lactic acid by oxidation and sufficient ATP is present all the reactions are reversible, and it is easy to see how the following series of reactions take place.

1. 2-phosphopyruvate $\rightleftharpoons$ 2-phosphoglycerate $\rightleftharpoons$ 3-phosphoglycerate
2. 3-phosphoglycerate + ATP $\rightleftharpoons$ 1,3-diphosphoglycerate + ADP
3. 1,3-diphosphoglycerate + ZH_2 $\rightleftharpoons$ 3-phosphoglyceric aldehyde + $HOPO_3^{=}$ + Z
4. 3-phosphoglyceric aldehyde $\rightleftharpoons$ phosphodihydroxyacetone
5. 3-phosphoglyceric aldehyde + phosphodihydroxyacetone $\rightleftharpoons$ fructose 1,6-diphosphate
6. fructose 1,6-diphosphate + AMP $\rightleftharpoons$ fructose 6-phosphate + ATP
7. fructose 6-phosphate $\rightleftharpoons$ glucose 6-phosphate
8. glucose 6-phosphate $\longrightarrow$ glycogen + $HOPO_3^{=}$ (see p. 390)

The conditions favoring these reactions from left to right, which corresponds to the synthesis of glycogen, should be clearly high concentrations of phosphopyruvate, ATP and ZH_2 (as compared with Z). In some way the oxidation of a portion of lactic acid by a series of reactions involving oxygen produces these conditions, of which the keeping up of the concentration of phosphopyruvate is probably the most important. How this is accomplished is still obscure but it would appear that oxalacetate is once again involved. We shall not attempt to depict the somewhat uncertain steps, but point out that the hydrogen required for step 3 above must come from the dehydrogenation of lactate. Removal of pyruvate in the following equilibrium

$$CH_3CHOHCOO^- + Z \rightleftharpoons CH_3COCOO^- + ZH_2$$

would accumulate ZH_2 for this reaction (the hydrogen atoms are attached to the prosthetic group of the enzyme, i.e., coenzyme I). So the oxidation of pyruvate would in a sense provide the energy required for one important part of the synthesis. *In this way one may regard the reformation of glycogen as a chemosynthesis from phosphopyruvate coupled with an oxidation of pyruvate.*

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The Assimilation of Carbon Dioxide. As already noted it has been recently discovered that carbon dioxide can be built back into complex molecules by living cells in the absence of light. This has been discovered by the use of carbon dioxide containing a carbon isotope (C^{11}, radioactive) in the presence of the enzyme systems (*in vivo*) which cause glycogen synthesis. The "tagged" carbon atoms are found in the glycogen. A detailed study shows that the carbon dioxide is first attached to pyruvic acid, forming the carboxyl group of oxalacetate. This substance is eventually converted to phosphooxalacetate through fumarate, and then to phosphopyruvate, the substance apparently needed in the resynthesis reactions just considered. This assimilation of carbon dioxide is clearly a chemosynthesis, the energy being derived from oxidation reactions. Tagged acetate ions have likwise been found to be synthesized into glycogen.

The absorption of carbon dioxide by pyruvate to form oxalacetate is probably a coupled reaction. It is unlikely that the equilibrium between the factors and the product is sufficiently favorable to allow any appreciable quantity of oxalacetate to be formed directly under the neutral conditions of the living cell. It will be recalled that reactions of the type $RCOOH \longrightarrow RH + CO_2$ run to completion in spite of the fact that they are slightly endothermic. The reaction $RCOO^- + H^+ \longrightarrow RH + CO_2$ is more nearly balanced at the concentration of hydrogen ion present under physiological conditions; indeed certain enolic substances absorb carbon dioxide at atmospheric pressure and in somewhat alkaline solution to form a potential carboxyl group. Thus resorcinol reacts with bicarbonate ion in aqueous neutral solution to form β-resorcylic acid (p. 504). However, unless the pyruvate-oxalacetate system has markedly different energy relations from those characteristic of this reaction, carbon dioxide at the low concentration present in the cell could hardly be absorbed without a coupled reaction. Probably an enolic derivative of pyruvate ion (such as 2-phosphopyruvate) absorbs carbon dioxide with liberation of a molecule of phosphate, the over-all reaction thus having a favorable equilibrium. The energy for the formation of the enolic derivative would, of course, come from degradation of the carbohydrate on oxidation as we have seen above.

Butyric Acid and Butanol Fermentations. Certain colorless simple organisms transform glucose to butyric acid while others form *n*-butanol. Both reactions occur under anaerobic conditions, and, like alcoholic fermentation and lactic acid formation, represent transforma-

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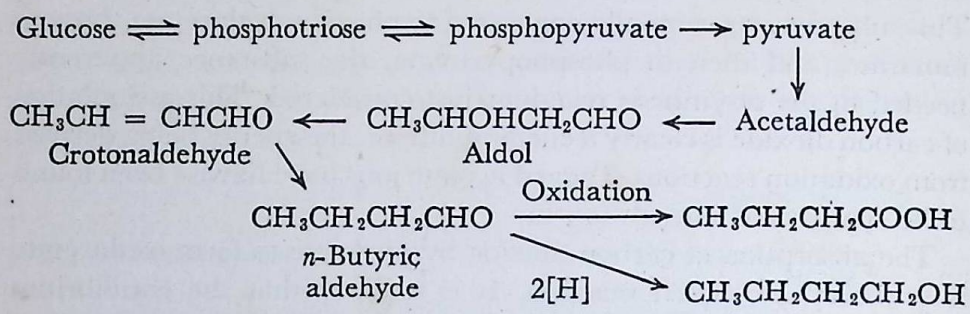
tions of glucose which yield energy. The exact mechanisms of the last steps in each process are not clear but pyruvate is again the key substance. As in the formation of ethyl alcohol, acetaldehyde may be formed first. If two molecules condense, crotonaldehyde would be produced via aldol. The hydrogenation of this aldehyde could yield *n*-butanol, its partial hydrogenation and oxidation (disproportionation) would yield butyric acid. Many other types of fermentations are



known, but these few which are of some industrial importance will illustrate the general types of reactions and their relation to the breakdown of glucose.

Photosynthesis. In spite of a great deal of experimentation and speculation about the mechanism of photosynthesis we are still far from having a clear picture of this essential biological process. Some of the earlier simple hypotheses, such as the assumption that formaldehyde is the first product, have been definitely disproved. Photosynthesis is certainly a complex process and involves at least four and perhaps many more steps in each of which an increment of radiant energy enters into the reaction. The green coloring material of all photosynthetic plants is essentially the same and is known as *chlorophyll* (p. 625). This material absorbs the radiant energy of sunlight; whether or not it also enters directly into a series of oxidation or reduction reactions is uncertain. The over-all reaction of photosynthesis is the hydrogenation (reduction) of carbon dioxide by water, the energy being supplied from outside. Until recently no evidence as to the intermediates was available; the first products to be identified were carbohydrates. Using radioactive carbon isotopes, however, it has been possible to show that in some plants the tagged carbon dioxide is absorbed in the absence of light with the formation of a carboxyl group. In the light this group disappears, probably through reduction. The absorption of carbon dioxide in the dark appears to be reversible.

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suggesting a mobile equilibrium for this step. The acid formed has a molecular weight of about a thousand. An attractive *hypothesis* suggests that in the presence of light the carboxyl group is reduced to an aldehyde and this in turn adds carbon dioxide in the dark, the process continuing until a triose is produced. The triose then splits off from the large parent molecule which is then free to begin the cycle again. Chemosynthetic reactions may well be coupled with the photosynthetic, and a number of steps must be involved as not enough energy can be absorbed at a time to complete the reduction of carbon-dioxide to the aldehyde stage.

The "dark reaction" in which carbon dioxide is fixed by a molecule of considerable size (mol. wt. ca. 1000) may represent a direct carboxylation, but is more likely another example of a coupled reaction. The concentration of carbon dioxide in the atmosphere is very small and it is difficult to imagine a carboxylation reaction with a sufficiently favorable equilibrium constant. An oxidation reaction may be coupled with this dark carboxylation to provide the necessary energy, as is probably the case in the formation of oxalacetate from pyruvate.

QUESTIONS AND PROBLEMS

1. Give several examples of enzyme reactions previously considered in this book.
2. What is the evidence that enzymes are proteins?
3. What are some of the characteristics of enzyme reactions?
4. What is meant by the phrases *in vivo* and *in vitro?* Illustrate by examples.
5. Explain the statement that "fermentation is life without oxygen."
6. Why is pyruvic acid often regarded as the key substance in the breakdown of carbohydrates? Outline the probable steps in its formation from glycogen in an active muscle in the presence of oxygen.
7. How is lactic acid formed in muscle tissue in the absence of oxygen?
8. What is the probable mechanism of the formation of ethyl alcohol from glucose in the presence of yeast cells?
9. How does the same process proceed when brought about by cell-free extracts of yeast?
10. How would you explain the formation of large quantities of glycerol when sugar is fermented by certain organisms?
11. What is the relation between the enzymatic conversion of glucose into ethyl alcohol on the one hand and into butyric acid on the other?
12. What is the evidence that the materials of which animal body is constituted are "perpetually in a state of flux"?
13. Compare and contrast photosynthesis and chemosynthesis.

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14. How have compounds containing an isotope of carbon been useful in elucidating the mechanism of biochemical processes?

15. Criticize the statement "Carbon dioxide is assimilated in nature only by the absorption of radiant energy in green plants."

16. What is meant by the phrase, "coupled reaction"? Give at least two examples.

17. How is some of the potential energy in glycogen made available for muscular work?

18. Write all the steps in the anaerobic glycolysis of glycogen.

19. Write all the steps in the process which is probably involved when lactic acid is oxidized in animal cells to carbon dioxide and water.

20. Under what conditions is glycogen synthesized in the animal body from lactic acid? By what steps does the process probably proceed?

21. What insight into the photosynthetic process has been obtained in recent years by the use of a radioactive isotope of carbon?

22. Define and illustrate the following terms: *metabolic rate*, *chemosynthesis*, *metabolic pool*, *dark reaction* (*photosynthesis*), *phosphorylation*, *catabolism*, *an energy-rich link*, *substrate*, *coenzyme*.

23. What appears to be the significance of oxalacetate in the complete oxidation of carbohydrates in animal tissue?

24. What is the significance of the pyrophosphate link in adenosine triphosphate? How is this substance related to the corresponding diphosphate and monophosphate?

25. Name four enzymes which have been isolated in the crystalline condition. What is the chemical reaction catalyzed by each?

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Chapter 21

BENZENE AND THE ALKYLBENZENES

Cyclic Compounds. In the preceding chapters we have considered for the most part compounds in which the carbon atoms were arranged in an open chain. In only a few instances, such as the cyclic anhydrides, have we encountered a substance whose structural formula contained a ring of atoms. The open-chain compounds are known as *aliphatic compounds* (fatty compounds). This name arose from the fact that the fatty acids (derived from the fats) are representatives of this class of substances.

In addition to these open-chain or aliphatic compounds a great variety of substances are known in which some of the atoms are combined in a ring. These **cyclic compounds** are divided into two classes, depending on whether or not the ring is composed entirely of atoms of the same kind. The **homocyclic compounds** contain only carbon atoms in the ring, while the **heterocyclic compounds** have atoms of other elements in the ring. The homocyclic compounds are for convenience further divided into two groups, namely, the **alicyclic compounds,** which resemble closely the aliphatic compounds, and the **aromatic compounds,** a group of substances containing a ring with a peculiar type of unsaturation. We shall consider at some length certain of these aromatic compounds in the next few chapters, since in both the scientific and industrial development of organic chemistry this class of substances has played a very important role.

The Development of Aromatic Chemistry. Certain hydrocarbons found in coal tar, notably benzene, C_6H_6, contain an aromatic ring. The chemistry of these hydrocarbons and the substances which can be prepared from them is called *aromatic chemistry.* The chemist's interest in aromatic chemistry has been connected with the industrial development of this subject during the last sixty years. The fact that certain substances can be readily and cheaply obtained from coal tar early led to their extensive study with a view to obtaining from them products of commercial importance. The efforts of the early investigators were richly rewarded as a great variety of dyestuffs, drugs, flavors

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and perfumes, photographic developers, and explosives were discovered. All these could be prepared from coal tar by relatively simple procedures. In order to appreciate and understand some of the triumphs of the organic chemist in this truly remarkable development we must acquaint ourselves with the general properties and behavior of that peculiar group of aromatic compounds which are found in coal tar.

The Refining of Coal Tar. The coal-tar dye industry may be considered as a byproduct of the steel industry. The distillation of coal yields coke, gas, ammonia, and coal tar. Coke is essential in the winning of iron from its ores and would be prepared for this purpose whether or not the coal tar were collected and utilized. Only a small fraction of the coal is obtained as coal tar and only a small portion of the coal tar is finally obtained as coal-tar crudes. From 100 lb of coal there is obtained 6 lb of coal tar and this furnishes only about ½ lb of coal-tar crudes. In spite of this very low yield, **benzene, toluene,** and **naphthalene** are cheap raw materials because an enormous amount of coal is each year converted into coke.

The refining of coal tar is done by distillation and by chemical treatment. The hydrocarbons are separated from each other by very efficient fractional distillation. Any basic nitrogenous material is removed by agitation with acid. **Phenol,** C_6H_5OH, and the **cresols,** $CH_3C_6H_4OH$, are weakly acidic compounds and are separated by shaking with sodium hydroxide solution. They pass into the aqueous layer and may then be obtained by acidification. The bulk of the tar is left as a black mass of pitch of unknown composition. It is used for roofing and for roads. The following diagram outlines the important steps.

1000 lb of coal tar

distilled | yields:

- Light oil redistilled yields approx.: → 16 lb Benzene, 2.5 lb Toluene, 0.3 lb Xylenes
- Middle oil extracted with NaOH and redistilled: → Phenol and cresols together about 20 lb; → Naphthalene 40 to 60 lb
- Heavy oil yields impure cresols and phenols
- Green oil yields anthracene and phenanthrene
- Pitch 500–600 lb

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In practice most of the light-oil fraction is obtained by scrubbing the gases evolved during the coking.

Coal-Tar Crudes. A number of substances may be obtained in a pure condition by the careful distillation of the light oil and middle

THE COAL-TAR CRUDES

Name	*Formula*	*Boiling Point*	*Melting Point*	*Solubility*
Benzene	C_6H_6	80°	+ 6°	All insoluble in water
Toluene	$C_6H_5CH_3$	111°	− 95°	
o-Xylene	$C_6H_4(CH_3)_2$	144°	− 27°	
m-Xylene	$C_6H_4(CH_3)_2$	139°	− 54°	
p-Xylene	$C_6H_4(CH_3)_2$	138°	+ 13°	
Naphthalene	$C_{10}H_8$	218°	+ 80°	
Anthracene	$C_{14}H_{10}$	342°	+218°	
Phenanthrene	$C_{14}H_{10}$	340°	+101°	

oil. For this purpose a still is employed which is equipped with a very efficient fractionating column. Those compounds which form a starting point for the synthesis of dyes, drugs, and explosives are called *coal-tar crudes*. The eight hydrocarbons given in the table above may be listed as being the most important coal-tar crudes.

In addition to the crudes listed in the table above, many more aromatic hydrocarbons, phenols, and heterocyclic compounds have been isolated from coal tar. Most of these are currently available only in experimental quantities, but they could be obtained in larger amounts if a demand for them arose.

BENZENE

The simplest of the aromatic compounds is benzene, C_6H_6. By studying this one substance we shall learn a great deal about the characteristics of the entire class. Benzene (sometimes called *benzol*) was discovered in 1825 by Faraday.[1] He obtained it by fractional distillation of an oil which was a byproduct of the manufacture of illuminating gas from whale oil. Twenty years later, the substance was

[1] Michael Faraday (1791–1867). Professor at the Royal Institution, London. First served as Sir Humphry Davy's assistant in the same laboratory. His researches on electricity and magnetism were of the greatest importance in the development of physics.

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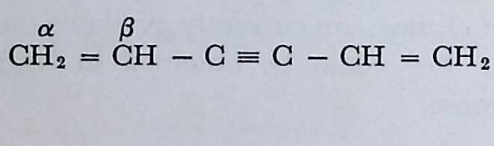
isolated from coal tar and its chemical investigation continued by A. W. Hofmann.[1]

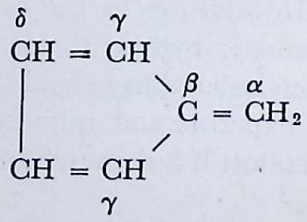
Structure of Benzene. The analysis and molecular weight of benzene correspond to the formula C_6H_6; it is thus a member of a series of hydrocarbons with the general formula C_nH_{2n-6}. Although the formula suggests that it is a highly unsaturated substance, it is very different indeed from an open-chain unsaturated hydrocarbon. *It reacts neither with bromine water nor potassium permanganate solution.* These two reagents, as we have seen, invariably react with aliphatic hydrocarbons having one or more CH=CH groups.

The failure of an apparently highly unsaturated hydrocarbon to enter into addition reactions is indeed surprising. But even more interesting and significant facts have been disclosed by a study of the products formed by replacing one hydrogen atom of benzene by another atom or group. All methods of preparing a compound with one such atom or group (a monosubstitution product) have yielded *only one substance*. For example, one and only one bromobenzene, C_6H_5Br, has ever been prepared. Many different methods have been employed which would have yielded isomeric bromobenzenes if such were possible. It is evident that in an open-chain compound such as represented by the formula I, or in an unsymmetrical ring compound, several monosubstitution products C_6H_5X, must exist.



I

Two isomers C_6H_5X; substituent on α or β atom



II

Three isomers C_6H_5X; substituent on atoms α, γ or δ

The only formula which is consistent with the fact that each hydrogen atom in benzene is equivalent to every other hydrogen atom is a formula having a symmetrical ring. The simplest formula meeting this condition is:

[1] August Wilhelm von Hofmann (1818–1892), (see p. 180, footnote). His study of the pure and applied chemistry of aromatic compounds was so important that he may be considered the founder of the coal-tar dye industry.

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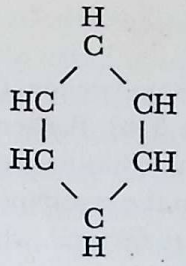
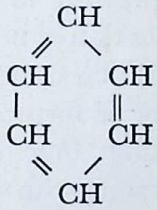
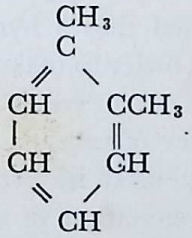


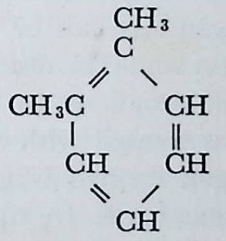
The Benzene Problem. The formula just written accounts for only three valences of each carbon atom. The simplest way to account for the remaining valence is to write alternate single and double bonds (formula I, below). Such a formula is symmetrical and, in agreement with experiment, calls for only one monosubstitution product, C_6H_5X. This formula has, however, two weaknesses: it is difficult to reconcile the presence of three double bonds with the inertness of benzene toward addition reactions; and the formula apparently predicts the existence of two isomeric disubstitution products in which the substituents are attached to adjacent carbon atoms (formulas II and III). Only one such disubstitution product is known.



I

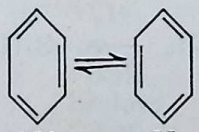


II



III

Kekulé, who proposed the hexagonal formula for benzene, suggested that the double linkages were constantly oscillating between the two positions shown in formulas IV and V. This would mean that the two disubstitution products II and III would exist as an equilibrium mixture and not as two separate substances.



IV V

The two formulas, IV and V above, differ from each other only in the position of valence electrons; the nuclei of all the atoms involved occupy the same positions in both formulas. This is the same situation

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which we encountered in the acetate ion, $CH_3\overset{\overset{\displaystyle O}{\|}}{C}-O^-$, and $CH_3\overset{\overset{\displaystyle O^-}{/}}{C}=O$, and the guanidinium ion (p. 338). Benzene therefore, like the acetate ion and the guanidinium ion, exhibits resonance; the forms IV and V are the contributing forms to the resonance hybrid which has a structure intermediate between them and which cannot be represented completely by either one. This interpretation of the structure of benzene is confirmed by the fact that in benzene all the carbon-carbon bonds are of the same length, 1.39Å, as compared with 1.54Å for a carbon-carbon single bond and 1.34Å for a carbon-carbon double bond.

Resonance is accompanied by increased stability and lowered reactivity. The resonance energy of benzene amounts to 34 to 36 kg-cal, and a consideration of the energy changes involved in addition to benzene shows why benzene is so unreactive toward addition. The reaction, benzene and hydrogen to form cyclohexadiene, absorbs heat to the extent of 5.8 kg-cal. According to our rule (p. 170) such a reaction would go to completion *to the left;* i.e., to form benzene and hydrogen. (It can be calculated that a hydrogen pressure of about 10^{11} atm would be necessary in order to make the reduction of benzene to cyclohexadiene go 90 per cent to completion.) When cyclohexadiene is treated with a number of catalysts, benzene is formed; the hydrogen formed is generally used in hydrogenating some of the cyclohexadiene. In the hydrogenation of cyclohexadiene to cyclohexene 26.5 kg-cal is evolved, and in the reduction of cyclohexene to hexahydrobenzene (cyclohexane) 28.2 kg-cal is liberated. These reactions, therefore, like the hydrogenation of open-chain ethylenic hydrocarbons, go to completion once started. The over-all reaction, benzene and hydrogen to form cyclohexane, evolves 48.9 kg-cal, and this process too, once started, will go to completion.

$$C_6H_6 \xrightarrow[\text{Heat absorbed 5.8 kg-cal}]{H_2} C_6H_8 \xrightarrow[\text{Heat evolved 26.5 kg-cal}]{H_2} C_6H_{10} \xrightarrow[\text{Heat evolved 28.2 kg-cal}]{H_2} C_6H_{12}$$

Over-all heat evolved 48.9 kg-cal

From these energy considerations it follows that the addition of two hydrogen atoms or their equivalent to benzene is impossible under

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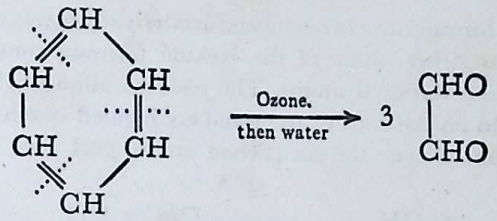
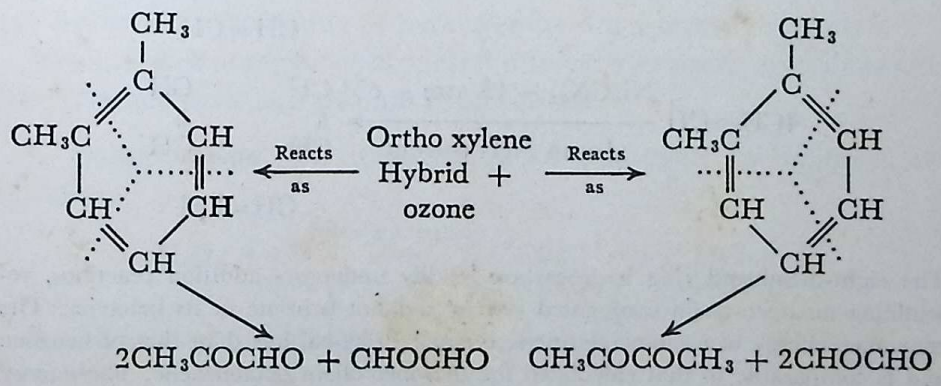
ordinary conditions, but that the addition of six hydrogen atoms or their equivalent should go to completion in the presence of suitable catalysts. These conclusions are consistent with the behavior of benzene. It is inert toward most addition reactions. A few reagents will add to benzene and, when they do add, the reaction goes through to the cyclohexane stage. Thus benzene can be reduced with hydrogen and a catalyst; the product is cyclohexane. Benzene combines with chlorine in direct sunlight to form the hexachloride, $C_6H_6Cl_6$ (see p. 574), and benzene reacts with ozone to furnish a triozonide which, on decomposition, yields glyoxal.



Resonance also offers a satisfactory explanation for the fact that isomers such as II and III above have never been isolated. The actual structure of ortho xylene does not correspond to either II or III, but is intermediate between them; almost as if there were a valence and a half between each pair of carbon atoms in the ring instead of alternate single and double bonds. Ortho xylene is then a single substance, the hybrid. But when it enters into reaction it does so as one or more of the contributing forms. On ozonization, therefore, ortho xylene furnishes glyoxal, methyl glyoxal, and diacetyl.



The formulation of benzene as a resonance hybrid is the current answer to a problem which has troubled chemists ever since Kekulé in 1866 proposed the hexagonal formula and suggested that the double bonds were in continual oscillation. Baeyer

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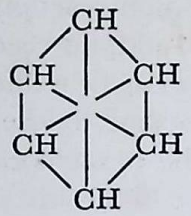
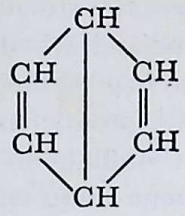
assumed that the fourth valence of each carbon atom was directed toward the center of the ring in a way that is peculiar to aromatic compounds. Dewar suggested a formula with a para bond.

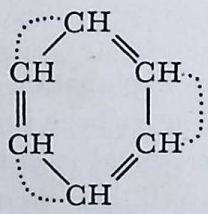


Baeyer centric formula

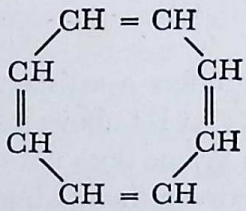


Dewar formula

Still another way of formulating benzene and its derivatives was suggested by Thiele. He pointed out that either phase of the Kekulé formula contained a conjugated system (p. 69) without terminal atoms. The residual affinity which he represented as being accumulated on the ends of the usual conjugated system was here imagined to be equally distributed over the six carbon atoms, and thus largely neutralized.

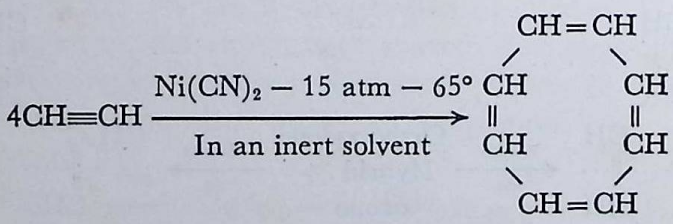


Thiele formula



Cyclo-octatetraene

Cyclo-octatetraene. This hydrocarbon presents the same problem as benzene. Cyclo-octatetraene was first prepared by Willstätter in very small amounts about forty years ago by a laborious degradation of a naturally occurring substance. It can now be made in any desired quantity from acetylene by a catalytic process.



The eight-membered ring hydrocarbon readily undergoes addition reactions, resembling an open-chain conjugated system and not benzene in its behavior. The resonance energy of cyclo-octatetraene is some 13 kg-cal less than that of benzene and is comparable to that calculated for the open-chain octatetraene. The energy relationships, therefore, are such as to permit with cyclo-octatetraene addition reactions which do not take place with benzene. The explanation for the smaller amount of resonance stabilization and the greater reactivity of cyclo-octatetraene is almost

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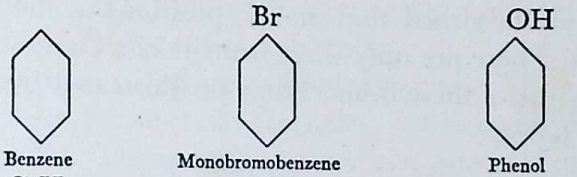
certainly to be found in the strain (p. 570) which would be present in a planar eight-membered ring. The large resonance energy of benzene is therefore a result not only of the symmetry of the molecule, for cyclo-octatetraene is also symmetrical, but also of the absence of strain in the six-membered planar ring.

Conventional Outline Formulas. For many practical purposes it makes little difference how we dispose of the extra valences in benzene, and, therefore, a method of writing formulas has been adopted which leaves the problem entirely unanswered. Benzene is represented by a hexagon; neither the carbon atoms nor the hydrogen atoms are written. It is assumed that the group CH constitutes each corner. If a group or atom has replaced a hydrogen, this group or atom is written. The following examples will make this clear.



Benzene C_6H_6 — Monobromobenzene C_6H_5Br — Phenol C_6H_5OH

In the formulas written above, it is immaterial whether the bromine atom and hydroxyl group are written at the top, side, or bottom of the hexagon. The ring is symmetrical and every position is equivalent to every other.

Aromatic Properties. The chemical properties which are characteristic of benzene and its derivatives are often spoken of as *aromatic properties.* These include: (*a*) resistance to oxidation; (*b*) acidic properties of the hydroxyl derivatives (to be discussed later); (*c*) failure to add reagents which usually add to the unsaturated compounds; (*d*) the ready substitution of hydrogen by other atoms or groups.

The last characteristic is of special interest and needs amplification. The characteristic substitution reactions are:

1. Halogenation, the substitution of hydrogen by chlorine or bromine.

$$C_6H_6 + \underset{(\text{or } Br_2)}{Cl_2} \xrightarrow{\text{Iron as a catalyst}} \underset{(\text{or } C_6H_5Br)}{C_6H_5Cl} + \underset{(\text{or } HBr)}{HCl}$$

2. Nitration, the substitution of hydrogen by the nitro group.

$$C_6H_6 + HNO_3 \xrightarrow{H_2SO_4} C_6H_5NO_2 + H_2O$$

A mixture of concentrated nitric and sulfuric acids is used.

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3. Sulfonation, the substitution of hydrogen by the sulfonic acid group.

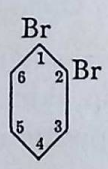
$$C_6H_6 + H_2SO_4 \longrightarrow C_6H_5SO_3H + H_2O$$

4. Friedel and Crafts[1] reaction, the introduction of an alkyl or acyl group by means of the halide and aluminum chloride.

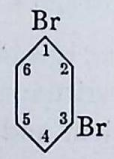
$$C_6H_6 + C_2H_5Br \xrightarrow{AlCl_3} C_6H_5C_2H_5 + HBr$$

$$C_6H_6 + CH_3COCl \xrightarrow{AlCl_3} C_6H_5COCH_3 + HCl$$

Number of Substitution Products. We have seen that it has been experimentally established that all the positions in the benzene ring are equivalent. There are only three isomers of a compound $C_6H_4X_2$. The nomenclature of these isomers may be illustrated by the dibromobenzenes, $C_6H_4Br_2$.



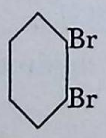
Ortho dibromobenzene or 1, 2-dibromobenzene



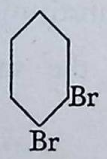
Meta dibromobenzene or 1, 3-dibromobenzene

Para dibromobenzene or 1, 4-dibromobenzene

The terms *ortho*, *meta*, and *para* should be noted. It is, of course, only the relative positions of the groups which is important, and the ortho compound, for example, may also be written:



or



There are three isomers of a trisubstituted benzene of the formula $C_6H_3X_3$. Thus, there are three tribromobenzenes.

[1] C. Friedel (1832–1899), a French chemist with whom the American J. M. Crafts (1839–1900) worked at the Sorbonne, Paris, in 1877. Crafts was professor of chemistry at the Massachusetts Institute of Technology.

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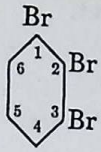
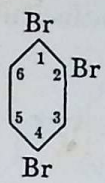
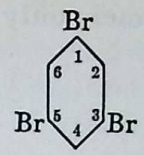


1, 2, 3-Tribromobenzene
(vicinal form)



1, 2, 4-Tribromobenzene
(asymmetric form)



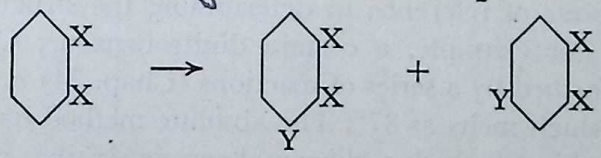
1, 3, 5-Tribromobenzene
(symmetric form)

Nomenclature of Polysubstituted Benzenes. The method of nomenclature which is used with benzene derivatives containing more than two groups involves the numbering of the ring as indicated above. The disubstitution products are also sometimes referred to in this way; thus, ortho dibromobenzene is 1,2-dibromobenzene, and the para compound 1,4-dibromobenzene.

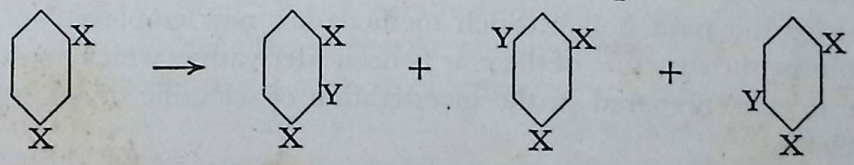
Determination of Positions of Substituents. Three and only three compounds with the formula $C_6H_4Br_2$, are known; the ortho, meta, and para isomers. The question now arises, how is it possible to decide which substance is ortho, which meta, and which para? A similar problem exists in regard to any benzene derivative with two or more substitutents. The actual steps in determining the structure of aromatic compounds are complicated and often difficult, but the general principle involved is very simple. By understanding this principle, we shall become acquainted with the fundamental basis for all the formulas of aromatic compounds which will be presented in the following chapters.

The ortho, meta, and para isomers differ in regard to the number of trisubstitution products which it is possible to prepare from them. This is illustrated below.

Ortho Isomer, two possible trisubstitution products.



Meta Isomer, three possible trisubstitution products.



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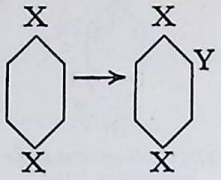
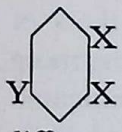
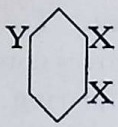
Para Isomer, only one trisubstitution product.



It must be remembered in this connection that such formulas as 

and 

are the same, though at first sight they appear different. (The two may be superimposed by rotating through 180° and folding the paper.) With this in mind one can easily convince oneself of the correctness of the propositions stated above by a few moments with a pencil and paper.

Returning now to the three isomeric dibromobenzenes, it is only necessary to take each isomer and determine the *maximum* number of substitution products $C_6H_3Br_2Y$ which can be prepared from it (where Y may be the NO_2 group, for example). The isomer which yields only one is the para, that yielding two is the ortho, and the third which yields three is the meta. This has been done by methods many of which will be considered in the following chapters; the results have established the structure of the isomers once and for all. Similar procedures with other isomeric compounds have yielded similar results. This is known as the *absolute method* of determining the position of groups. It was first employed by Körner,[1] and one of the cases studied by him was that of the dibromobenzenes.

After the structure of a number of aromatic compounds had been established by the absolute method, it was possible to use these substances as points of reference in determining the structure of other compounds. For example, a certain dinitrobenzene, $C_6H_4(NO_2)_2$, can be transformed by a series of reactions (Chap. 24) into the dibromobenzene which melts at 87°. The absolute method had previously shown that this particular dibromobenzene is the para isomer. Therefore, the dinitrobenzene, which could be transformed into it, was also the para isomer. Such methods are now employed in determining the structure of the new benzene derivatives which are from time to time prepared in the investigation of scientific or industrial problems.

[1] Wilhelm (Guglielmo) Körner, 1839–1925, professor at Milan.

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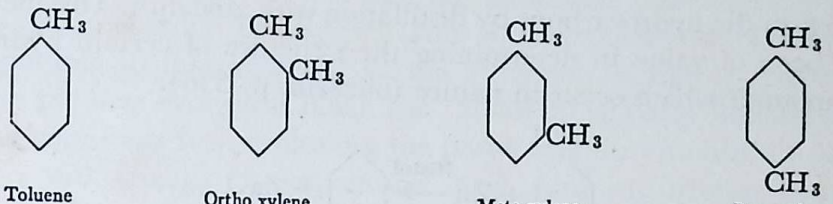
ALKYL DERIVATIVES OF BENZENE

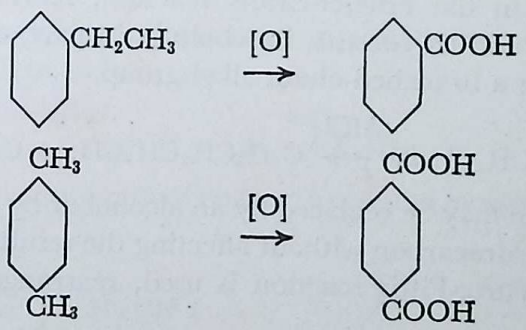
The alkyl derivatives of benzene are very similar to the parent substance in their general behavior. Toluene, $C_6H_5CH_3$, and the isomeric xylenes are readily obtained from coal tar. We shall have many occasions to refer to toluene since it can be transformed into a variety of important substances. The structures of toluene and of the three isomeric xylenes are as follows:



Toluene — Ortho xylene — Meta xylene — Para xylene

The boiling points of the three isomeric xylenes lie so near together that it is difficult to separate the one from the other. Commercial xylene is a mixture of all three. The separation of a mixture of ortho, meta, and para isomers is a difficult operation and requires very efficient fractional distillation or repeated crystallization unless hydrogen bonding or chelation occurs, in which event the separation is relatively easy. See p. 439.

The alkyl benzenes show even more strikingly than benzene itself the resistance of the aromatic nucleus to oxidation. Many alkyl benzenes, regardless of the length of the alkyl group, can be oxidized to aromatic acids (p. 498); in this process the saturated aliphatic side chain, not the unsaturated aromatic ring, is attacked.



Methods of Preparing Aromatic Hydrocarbons. Although benzene, toluene, and the xylenes are obtained from coal tar, it is important to have general methods of preparing aromatic hydrocarbons. Some of these are very similar to the methods used for preparing aliphatic hydrocarbons. For example, the sodium salts of aromatic

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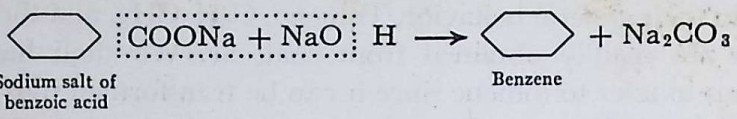
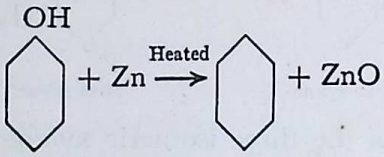
acids on heating with sodium hydroxide yield the corresponding hydrocarbon.



The hydroxyl derivatives of aromatic hydrocarbons may be reduced to the hydrocarbons by distillation with zinc dust. This method has been of value in determining the structure of certain hydroxyl compounds which occur in nature (alizarin, p. 556).



The introduction of alkyl groups into the aromatic ring (or *nucleus* as it is often called) may be accomplished by the Friedel-Crafts reaction previously mentioned (p. 410), or by the Wurtz-Fittig reaction. When the Friedel-Crafts reaction is employed to introduce straight-chain alkyl groups it is necessary to introduce an acyl group first and then reduce it by methods to be described later (p. 492).

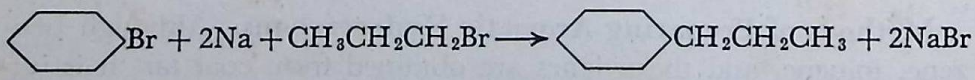
$$C_6H_6 \xrightarrow[AlCl_3]{CH_3CH_2COCl} C_6H_5COCH_2CH_3 \xrightarrow[HCl]{Zn-Hg} C_6H_5CH_2CH_2CH_3$$

When a straight-chain alkyl halide containing more than two carbon atoms is used in the Friedel-Crafts reaction, rearrangement takes place and the product consists, in whole or in part, of an alkyl benzene containing a branched-chain alkyl group.

$$C_6H_6 + CH_3CH_2CH_2Br \xrightarrow{AlCl_3} C_6H_5CH_2CH_2CH_3 + C_6H_5CH(CH_3)_2$$

The alkyl halide may be replaced by an alcohol or by the corresponding ethylenic hydrocarbon without affecting the result of the reaction.

When the Wurtz-Fittig reaction is used, rearrangement does not take place.



Preparation of Aromatic Hydrocarbons from Aliphatic Compounds. When *n*-heptane is heated in the presence of suitable catalysts, conversion to toluene and hydrogen occurs.

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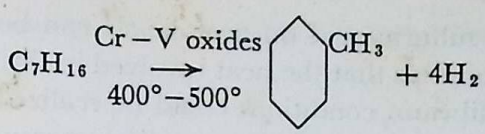


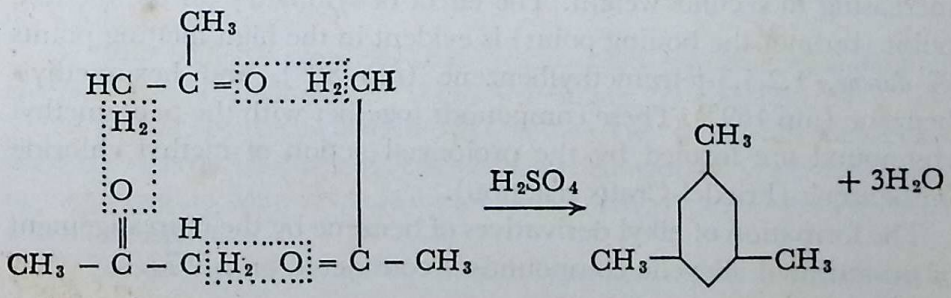
This reaction from left to right is *endothermic* by about 60 kg-cal. Therefore in the presence of a suitable catalyst it should go completely to the left at room temperature. Because there are five molecules on one side of the equation and one on the other, however, the very large heat evolution corresponds only to a completeness of reaction comparable to that observed in the reduction of simple ethylenes, where the heat evolved is much less (about 30 kg-cal.). But, because of the very large heat evolution, the position of the equilibrium shifts *rapidly* with change of temperature. And, since an increase in temperature shifts the equilibrium in favor of the endothermic reaction, it is possible at about 500° in the presence of a catalyst to convert heptane to toluene and hydrogen. The same process is applicable, of course, to heptene, while hexane and hexene yield benzene.

This process whereby paraffin hydrocarbons are converted to aromatic hydrocarbons attained extraordinary importance in World War II, and petroleum as a source of toluene for nitration to TNT (p. 438) far outstripped coal tar. In 1940 no commercial production of nitration-grade toluene from petroleum was reported; by 1944 the toluene obtained from petroleum amounted to 70 per cent of all that produced in this country. The fact that there was an adequate supply of toluene for TNT during World War II is the direct result of the development of the process we have been considering for, while the production of toluene from coal tar increased only from 30,000,000 gal in 1940 to 38,000,000 gal in 1944, the production of toluene from petroleum increased from none to 96,000,000 gal in the same period.

Of much less practical importance in this country is the polymerization of acetylene to benzene.

$$3CH \equiv CH \xrightarrow{500^\circ} C_6H_6$$

The symmetrical trimethylbenzene, known as *mesitylene*, is prepared



1, 3, 5-Trimethylbenzene
or mesitylene

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by the action of sulfuric acid on acetone. It can be estimated from the energy relationships that the heat involved in this reaction is large and that, if equilibrium conditions could be realized, the concentration of acetone would be much too small to measure (far less than 0.00001 per cent).

Higher Homologs of Toluene. The physical properties of some of the simpler alkyl derivatives of benzene are given in the accompanying table.

PHYSICAL PROPERTIES OF SOME ALKYL DERIVATIVES OF BENZENE

Name	*Formula*	*Melting Point*	*Boiling Point*	*Density at 20°*
Toluene	$C_6H_5CH_3$	− 92.4°	111°	0.865
Ortho xylene	$C_6H_4(CH_3)_2$	− 28°	142°	0.863
Meta xylene	$C_6H_4(CH_3)_2$	− 54°	140°	0.865
Para xylene	$C_6H_4(CH_3)_2$	+ 15°	138°	0.863
Ethylbenzene	$C_6H_5C_2H_5$	− 94°	135°	0.876
Propylbenzene	$C_6H_5CH_2CH_2CH_3$			
Isopropylbenzene (Cumene)	$C_6H_5CH(CH_3)_2$		150°	
Pseudocumene	$C_6H_3(CH_3)_3$-1,2,4	− 45°	169°	
Mesitylene	$C_6H_3(CH_3)_3$-1,3,5	− 53°	165°	
1,2,3,5-Tetramethylbenzene	$C_6H_2(CH_3)_4$	below 0°	195°	
1,2,3,4-Tetramethylbenzene	$C_6H_2(CH_3)_4$	− 4°	204°	
1,2,4,5-Tetramethylbenzene (Durene)	$C_6H_2(CH_3)_4$	+79−80°	194°	
1,2,3,4,5-Pentamethylbenzene	$C_6H(CH_3)_5$	+ 53°	231°	
Hexamethylbenzene	$C_6(CH_3)_6$	+169°	264°	

In general, both the boiling point and melting point increase with increasing molecular weight. The effect of symmetry on the melting point (but not the boiling point) is evident in the high melting points of *durene*, 1,2,4,5-tetramethylbenzene (mp 80°), and hexamethylbenzene (mp 169°). These compounds together with the pentamethyl compound are formed by the prolonged action of methyl chloride on benzene (Friedel-Crafts reaction).

The formation of alkyl derivatives of benzene by the rearrangement of unsaturated alicyclic compounds is considered on p. 577.

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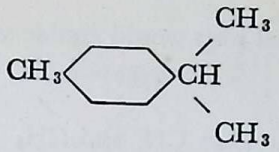
Cymene (or para cymene), 1-methyl-4-isopropylbenzene,



is closely related to a number of the terpenes which are considered in Chap. 30. Many terpenes may be converted into this hydrocarbon (p. 581). It occurs in a variety of essential oils. The structure of cymene was established by synthesis early in the development of the theory of structure. This established the nature of the carbon skeleton in those terpenes which could be transformed into it.

Nomenclature of Aryl Groups. Just as we have names for the alkyl groups, so it is convenient to have names for the groups corresponding to an aromatic radical—aryl groups. The aryl group, C_6H_5-, is known as the *phenyl group*. The name originated from the fact that the corresponding hydroxyl compound, C_6H_5OH, is known as *phenol*. It must be noted that the name of this aryl group does not suggest the name of the corresponding hydrocarbon. However, the nomenclature of the aryl groups corresponding to the alkyl derivatives of benzene usually follows that of the hydrocarbon. Thus, $CH_3C_6H_4-$ is the tolyl group (ortho, para, or meta), $(CH_3)_2C_6H_3-$, the xylyl group, and $(CH_3)_3C_6H_2-$, the mesityl group. The group, $CH_3C_6H_4-$, is also sometimes called the *cresyl group*, the name being derived from that of the hydroxyl compound, $(CH_3C_6H_4OH)$, cresol.

QUESTION AND PROBLEMS

1. Write structural formulas for ortho xylene, 1,2,4-trimethylbenzene, 2-bromo-1,3-dimethylbenzene, vicinal trichlorobenzene, para bromotoluene, meta chlorobromobenzene, mesitylene, and para cymene.

2. What products would you expect to obtain from the action of ozone on 1,2-dichlorobenzene?

3. Write balanced equations for the reaction between benzene, aluminum chloride, and (*a*) ethyl alcohol, (*b*) ethyl bromide, (*c*) ethylene.

4. Why is the reaction described in Question 3 not satisfactory for preparing other *n*-alkyl derivatives of benzene than ethylbenzene? Outline the steps in the procedure you would use for preparing *n*-butylbenzene from benzene and butyl alcohol.

5. Discuss the preparation of aromatic hydrocarbons from petroleum.

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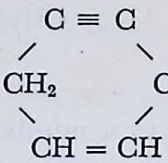
6. What facts make it necessary to write a symmetrical structural formula for benzene?

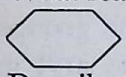
7. What simple chemical tests would enable you to distinguish between benzene, $CH_3CH_2C \equiv C - C \equiv CH$, and



8. Compare the chemical behavior of benzene and ethylene.

9. Write structural formulas for all the dichlorobenzenes and the trichlorobenzenes.

10. How many isomeric tetramethylbenzenes and pentamethylbenzenes should there be?

11. What reactions would you use to show that an organic compound was either  CH_2CH_3 or CH_3 CH_3?

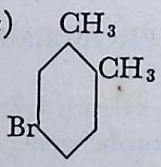
12. Describe briefly the refining of coal tar, and name the important coal-tar crudes.

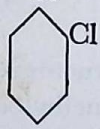
13. Define and illustrate with examples the following terms: (*a*) *homocyclic*, (*b*) *orientation*, (*c*) *alicyclic*, (*d*) *aryl*, (*e*) *heterocyclic*.

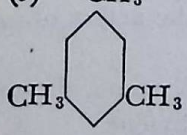
14. List six reactions which benzene and its homologs may undergo. Predict, if possible, the behavior of olefins in each of the reactions listed.

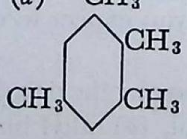
15. Write equations indicating what occurs when the following are allowed to react: (*a*) *o*-bromotoluene, isopropyl bromide, and sodium; (*b*) benzene, acetyl chloride, and aluminum chloride; (*c*) benzene, chlorine, and sunlight; (*d*) acetone and concentrated sulfuric acid.

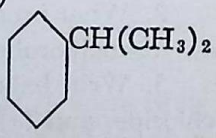
16. How many products would one expect to be formed by nitrating the following substances?

(*a*) 

(*b*) 

(*c*) 

(*d*) 

(*e*) 

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Chapter 22

ARYL HALIDES, SULFONIC ACIDS, AND PHENOLS

ARYL HALIDES

One of the characteristic reactions of aromatic compounds is the replacement of a hydrogen atom on the ring by chlorine or bromine. The resulting compounds are **aryl halides.** Unlike the alkyl halides, the simple aryl halides are almost never prepared from the corresponding hydroxyl compounds. They are usually prepared from the hydrocarbons. The following table lists some of the more important aryl halides; they are all insoluble in water and heavier than water.

CHLORO, BROMO, AND IODO DERIVATIVES OF BENZENE AND TOLUENE

Name	*Formula*	*Boiling Point*	*Melting Point*
Chlorobenzene	C_6H_5Cl	132°	−45°
Bromobenzene	C_6H_5Br	156°	−31°
Iodobenzene	C_6H_5I	189°	−31°
o-Chlorotoluene	$CH_3C_6H_4Cl(o)$	159°	−35°
m-Chlorotoluene	$CH_3C_6H_4Cl(m)$	162°	−48°
p-Chlorotoluene	$CH_3C_6H_4Cl(p)$	163°	+ 8°
o-Bromotoluene	$CH_3C_6H_4Br(o)$	182°	−28°
m-Bromotoluene	$CH_3C_6H_4Br(m)$	184°	−40°
p-Bromotoluene	$CH_3C_6H_4Br(p)$	184°	+28°
o-Iodotoluene	$CH_3C_6H_4I(o)$	211°	——
m-Iodotoluene	$CH_3C_6H_4I(m)$	204°	——
p-Iodotoluene	$CH_3C_6H_4I(p)$	212°	35°

Chlorobenzene and Bromobenzene. These two substances may be taken as typical representatives of the aryl halides. They are prepared by the action of chlorine or bromine on warm benzene in the presence of some catalyst. Iron is almost always the catalyst employed.

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$$C_6H_6 + Br_2 \xrightarrow{Fe} C_6H_5Br + HBr$$

The product is purified by distillation. In addition to the monohalogen compound, some dichloro- or dibromobenzene is also formed. Unlike bromine and chlorine, iodine, by itself, does not directly replace a hydrogen atom attached to an aromatic ring. Iodobenzene, however, can be made by the action of iodine and boiling nitric acid on benzene.

$$2C_6H_6 + 2I + [O] \xrightarrow{HNO_3} 2C_6H_5I + H_2O$$

Halogenation of Alkyl Derivatives of Benzene. The alkyl derivatives of benzene such as toluene and ethylbenzene may react in two different ways when treated with chlorine or bromine. A hydrogen atom of the nucleus or a hydrogen atom of the alkyl group (the "side chain") may be replaced. The nuclear halogenation is accelerated by such catalysts as metallic iron or ferric salts; the introduction of a halogen atom into the side chain is favored by strong light and high temperature.

$$C_6H_5CH_3 + Cl_2 \xrightarrow[FeCl_3]{\text{Catalyst}} \underset{\text{Mixture of ortho and para isomers}}{ClC_6H_4CH_3} + HCl$$

$$C_6H_5CH_3 + Cl_2 \xrightarrow{\text{Light}} \underset{\text{Benzyl chloride}}{C_6H_5CH_2Cl} + HCl$$

It will be noticed that the product of the side-chain chlorination, **benzyl chloride** (bp 179°), does not contain the halogen atom directly attached to the aromatic ring. It is, therefore, not an aryl halide like ortho and para chlorotoluene but an alkyl halide (methyl chloride) in which one hydrogen atom has been replaced by an aromatic group (C_6H_5).

The chlorination of the side chain of toluene proceeds further to give **benzal chloride** (bp 207°), $C_6H_5CHCl_2$, and finally **benzotrichloride** (bp 213°), $C_6H_5CCl_3$. Unlike the chlorination of methane (p. 43), the side-chain reaction of toluene with chlorine can be controlled so that any one of the three chlorination products can be obtained in a good yield.

$$C_6H_5CH_2Cl + Cl_2 \longrightarrow \underset{\text{Benzal chloride}}{C_6H_5CHCl_2} + HCl$$

$$C_6H_5CHCl_2 + Cl_2 \longrightarrow \underset{\text{Benzotrichloride}}{C_6H_5CCl_3} + HCl$$

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Dichlorobenzenes. On chlorination of chlorobenzene in the presence of iron three disubstitution products are obtained: ortho, 39 per cent (mp −17.6°, bp 179°); meta, 5 per cent (mp −24.8°, bp 173°); para, 55 per cent (mp 56°, bp 174°). Para dichlorobenzene is used extensively as a moth and caterpillar repellant.

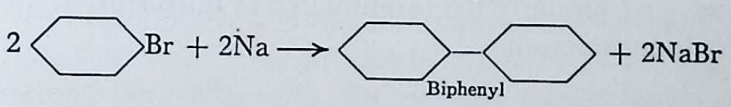
Chemical Behavior of Aryl Halides. In comparison with the alkyl halides, the aryl halides are very unreactive; for example, they do not react with potassium cyanide, silver hydroxide, or, under the usual conditions employed in the laboratory, with sodium hydroxide or ammonia. When heated under pressure to 200° to 300° with these last two reagents and copper salts, the halogen atom may be replaced by the hydroxyl and amino groups respectively.

Aryl halides react with magnesium to form a Grignard reagent which is similar to the aliphatic Grignard reagents.

$$C_6H_5Br + Mg \xrightarrow[\text{ether}]{\text{Dry}} C_6H_5MgBr$$

Aryl halides react with metallic sodium in the Wurtz-Fittig reaction considered in the last chapter. If no alkyl halide is employed two molecules of the aryl halide join together.

$$C_6H_5Br + C_2H_5Br + 2Na \longrightarrow \underset{\text{Ethylbenzene}}{C_6H_5C_2H_5} + 2NaBr$$



It is interesting to recall that the halogen derivatives of unsaturated aliphatic hydrocarbons, such as vinyl bromide, $CH_2 = CHBr$, are also unreactive (p. 305) and, in this respect, resemble the aryl halides. A consideration of the formula for benzene suggests a reason for this striking analogy. A halogen atom directly attached to an unsaturated atom is unreactive; the nuclear atoms in benzene are unsaturated and hence the aryl halides do not readily enter into metathetical reactions.

Formation of Ortho, Meta, and Para Isomers. In the preparation of the disubstitution products of benzene, three isomers are possible. For example, the further bromination of bromobenzene might yield the ortho or the meta or the para isomer. Actually, the product is a mixture of the ortho and para compounds. By contrast, the bromination of nitrobenzene, $C_6H_5NO_2$, yields the meta bromonitrobenzene. Some rules for predicting the isomers are obviously needed.

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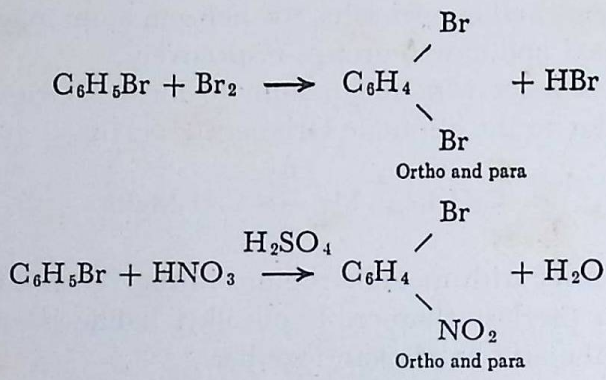
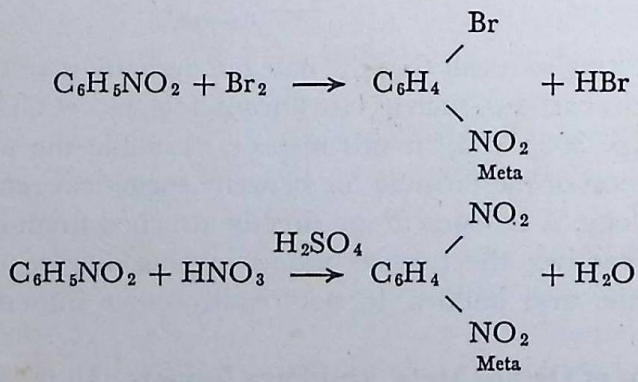
The Directive Influence of Substituents. An exhaustive study of the preparation of disubstituted benzenes has led to *two important generalizations*. These are subject to certain reservations but are nevertheless of great value as an approximate guide in predicting the course of substitution reactions. The first generalization is as follows: *the position of the entering group is determined by the nature of the atom or group already present* and is independent of the nature of the entering group. For example, the bromination of bromobenzene yields a mixture of the ortho and para compounds, and the nitration of bromobenzene proceeds in the same way.



On the other hand, the nitration of nitrobenzene yields only the meta compound, and similarly the bromination of nitrobenzene yields only meta bromonitrobenzene.



Rules of Orientation. It will be seen from the above examples that the directing influences of the bromine atom and the nitro group are different. One causes the formation of a mixture of ortho and para isomers, the other only of the meta compound. It has been found that all the atoms or groups which are common substituents in the benzene

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ring may be divided into two categories according to whether they have a directive influence like that of the bromine atom or like that of the nitro group. This is the second great generalization in regard to substitution in aromatic compounds.

A list of the groups is given below.

Class I. (Directs the entering group into the ortho and para positions.) OH, NH_2, OCH_3, $N(CH_3)_2$, $NHCOCH_3$, Cl, Br, I, CH_3 and other alkyl groups, CH_2COOH.

Class II. (Directs the entering group into the meta position.) NR_3^+, NO_2, $C \equiv N$, COOH, SO_3H, $COOC_2H_5$, CHO, COR, NH_3^+.

Those atoms and groups in Class I are spoken of as *ortho and para orienting atoms or groups;* those in Class II as *meta orienting groups.* It will be convenient to remember that all those groups which contain a double linkage *connected to the first atom* fall in Class II as do those which carry a positive charge on the atom directly attached to the ring. In general, the introduction of a second substituent into a molecule is easier (i.e., proceeds more rapidly at a lower temperature) if the substituent already present belongs to Class I, and is more difficult when the substituent present is of Class II.

Limitations of the Rules. Several important exceptions to these rules of orientation will be noted even in this elementary presentation of the subject; if a greater number of aromatic compounds were considered, the exceptions would be more numerous. Not only are there certain cases where the facts are exactly contrary to the simple rules of orientation, but, in general, the *rule only predicts the major product of the reaction.* There is, almost always, at least a few per cent of the other isomers formed. In spite of these limitations, the rules of orientation are of invaluable assistance in the practical matter of devising syntheses of aromatic compounds with several groups. We shall repeatedly refer to them.

Factors Influencing the Proportions of Isomers. We have just seen that the major course of a substitution reaction is determined by the nature of the group already attached to the ring. Relatively minor variations in the proportions of the isomers, however, are affected by the nature of the entering group. For example, bromobenzene, on chlorination, bromination, and nitration yields predominantly a mixture of ortho and para isomers as predicted by the general rules. The small amount of meta isomer produced varies, however, from a minimum of 0.3 per cent in the nitration to a maximum of 6 per cent in the chlorination (using iron as a catalyst). The variations in the ratio of para to ortho isomer are shown by the following tabulation:

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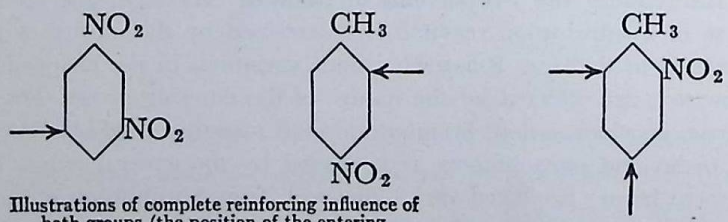
RATIO OF PARA TO ORTHO ISOMER FORMED ON INTRODUCING A SECOND GROUP INTO BROMOBENZENE

Second group:	Br	Cl	NO_2
Ratio of para to ortho isomer:	6.4	1.2	1.7

The conditions under which the reaction is carried out also often have an important effect on the proportion of isomers. For example, the chlorination of chlorobenzene using aluminum chloride as a catalyst yields more than twice as much para as ortho compound (66:30); with ferric chloride the two isomers are formed in more nearly equal amounts (55:40). The temperature may affect the relative amounts of isomers. This is particularly true of nitration and sulfonation. For example, the sulfonation of toluene at 0° yields the ortho and para isomers in approximately equal amounts with about 4 per cent of the meta isomer; at 100°, the three toluene sulfonic acids are formed in the proportions 73 of para to 17 of ortho to 10 of meta.

Introduction of a Third Substituent. The rules of orientation are not confined to the formation of disubstitution products. With certain qualifications they are also applicable to the prediction of the position taken by an entering group in the formation of higher substitution products. Experiment has shown that the effect of two or more groups may be predicted from a knowledge of the orienting influence of each group alone and an estimate of the relative orienting strength of the group. The common groups are usually given in the following order, the first having the strongest influence: (A) Class I, OH and NH_2 > CH_3CONH > Cl > I > Br > CH_3; (B) Class II, NO_2 > COOH > SO_3H. The prediction also depends on the relative position of the groups already present for this determines whether their orienting influences will reinforce each other or will compete. Thus two meta orienting groups in the meta position to each other will cause a third substituent to take position 5, and the amount of ortho isomer formed will be very small indeed. Similarly when an ortho-para orienting group is para or ortho to a meta orienting group, both groups direct the entering substituent into the same positions.



Illustrations of complete reinforcing influence of both groups (the position of the entering group is shown by the arrow).

If the influence of the two groups is directed to different atoms then the possibility is present of forming a number of isomers. For example,

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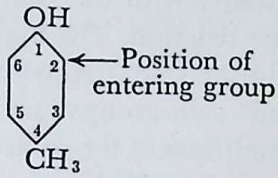
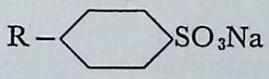
in a molecule in which two similar groups (of either class) are in the ortho or para position to each other, the directive influences are such that every unoccupied position in the benzene nucleus may be substituted. However, experiments have shown that the position of the substitution is then determined by the relative influence of the two groups. For example, in the nitration of para cresol the entering group takes the position ortho to the hydroxyl group whose orienting influence is greater than that of the methyl group.



ARYL SULFONIC ACIDS

Aryl Sulfonic Acids. One of the characteristic reactions of aromatic compounds mentioned in the previous chapter is sulfonation. The product of this reaction is an aryl sulfonic acid, which is usually isolated as a salt. The aryl sulfonic acids are of importance in the preparation of other compounds since the sulfonic acid group may be replaced by other groups. The sulfonic acid group is also often introduced into a molecule in order to make the compound soluble in water. The aryl sulfonic acids of low molecular weight and most of their salts are soluble in water. Even some aromatic hydrocarbons of very complex structure and high molecular weight may be changed into water-soluble products by the introduction of a number of sulfonic acid groups.

One group of detergents (p. 213) is made by chlorinating high-boiling petroleum fractions and treating the resulting alkyl chlorides with benzene and aluminum chloride. This furnishes alkyl benzenes containing a long-chain alkyl group, R. When these substances are sulfonated, the sodium salts of the sulfonic acids are detergents.



Sulfonation of Aromatic Hydrocarbons. The sulfonation of benzene is typical of the procedure employed in the preparation of an aryl sulfonic acid and the isolation of the sodium salt. In the usual procedure benzene is agitated with a large excess of sulfuric acid kept somewhat above room temperature.

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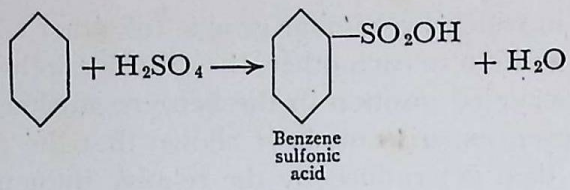
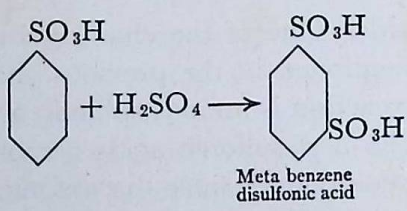


The rate of the reaction depends on the concentration of the sulfuric acid and the temperature. The water formed in the process decreases the speed by diluting the acid. If sulfur trioxide is present (as in *fuming* sulfuric acid), it unites with the water and keeps the reagent anhydrous throughout the reaction. The higher the temperature and the more sulfur trioxide in the acid, the more rapid is the sulfonation. One, two, or three sulfonic acid groups may be introduced into benzene depending on the conditions of the reaction. There is no difficulty in controlling the process so that either the mono- or the disulfonic acid is the sole product.



The aryl sulfonic acids are nonvolatile solids which are soluble in water and insoluble in most organic solvents. Because of this, the isolation of the sulfonic acids from the reaction mixture which contains a large amount of sulfuric acid requires a rather special method. Advantage is taken of the fact that the calcium, barium, or lead salts of sulfonic acids are soluble in water. Hence, the reaction mixture is first diluted with water, neutralized with lime (a process known in industry as *liming out*), and filtered. The filtrate of this mixture contains the calcium salt. The calcium salts of the sulfonic acids are readily converted to sodium salts by treatment with sodium carbonate.

Isolation and Properties of Free Sulfonic Acids. The free aromatic sulfonic acids are rarely isolated and are very little employed as such. They may be obtained from the calcium, barium, or lead salts by adding the calculated quantity of sulfuric acid, filtering the insoluble inorganic sulfate, and concentrating the solution. They are solids usually crystallizing with water of crystallization and frequently are hygroscopic. They are very soluble in water and to a slight extent in some organic solvents. The sulfonic acids are as strong as the mineral acids. Benzene sulfonic acid and the toluene sulfonic acids are sometimes employed as catalysts in reactions where a strong, nonvolatile acid is required, as in the dehydration of alcohols to form olefins (p. 52).

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Reactions of Sulfonic Acids and Sulfonates. The sulfonic acid group may be replaced by the hydroxyl group, the nitrile group, or hydrogen. All these reactions are of importance in the preparation of aromatic compounds. They are illustrated by the following representative equations.

1. Replacement by OH.

$$C_6H_5SO_3Na + 2NaOH \xrightarrow[\text{Molten}\quad 300^\circ]{} C_6H_5ONa + Na_2SO_3 + H_2O$$

$$C_6H_5ONa + H_2SO_4 \longrightarrow \underset{\text{Phenol}}{C_6H_5OH} + NaHSO_4$$

2. Replacement by C ≡ N.

$$C_6H_5SO_3Na + NaCN \longrightarrow \underset{\text{Benzonitrile}}{C_6H_5CN} + Na_2SO_3$$

3. Replacement by H.

$$C_6H_5SO_3H + H_2O \xrightarrow[\text{On heating at about 150° with dilute acid under pressure}]{} C_6H_6 + H_2SO_4$$

The acid chlorides of the aryl sulfonic acids are formed by the action of the chlorides of phosphorus on the free acids or the sodium salts.

$$C_6H_5SO_3Na + PCl_5 \longrightarrow C_6H_5SO_2Cl + NaCl + POCl_3$$

Aryl Sulfonamides. The action of ammonia on the aryl sulfonyl chlorides yields the unsubstituted aryl sulfonamides. These are crystalline solids; benzene and toluene sulfonamides are somewhat soluble in organic solvents and in water. The para toluene sulfonamide, $CH_3C_6H_4SO_2NH_2$, is a byproduct of the manufacture of saccharin (p. 509). The sulfonamides which contain a replaceable hydrogen atom dissolve in aqueous sodium hydroxide forming salts.

$$C_6H_5SO_2NH_2 + NaOH \longrightarrow C_6H_5SO_2NHNa + H_2O$$

On acidifying, the sulfonamide is precipitated. The aryl sulfonyl group (e.g., $C_6H_5SO_2-$), is very acidic in its influence. The corresponding OH compounds (the sulfonic acids) are strong acids and the $-NHR$ derivatives are strong enough acids to dissolve in aqueous sodium hydroxide. (It will be recalled that the amides of the organic acids were not acidic enough to manifest this property in aqueous solution, p. 180.)

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The **chlorosulfonamides** are interesting compounds prepared by the action of sodium hypochlorite on the sulfonamides.

$$CH_3C_6H_4SO_2NH_2 + NaOCl \longrightarrow CH_3C_6H_4SO_2NHCl + NaOH$$

They are crystalline solids which in water solution slowly liberate hypochlorous acid.

$$CH_3C_6H_4SO_2NHCl + H_2O \xrightarrow[\text{Slowly}]{} CH_3C_6H_4SO_2NH_2 + HOCl$$

For this reason they have been used as effective antiseptic agents for wounds. Chloramine T is a sodium salt, $CH_3C_6H_4SO_2NClNa$, and is soluble in water: dichloramine T is $CH_3C_6H_4SO_2NCl_2$, and is soluble in organic solvents.

Benzene Sulfonyl Chloride as a Reagent for Amines. Like other acid chlorides, the chlorides of the aryl sulfonic acids will react with water, alcohols, or amines. The reactions with benzene sulfonyl chloride are:

$$C_6H_5SO_2Cl + H_2O \longrightarrow C_6H_5SO_3H + HCl$$
$$C_6H_5SO_2Cl + CH_3OH \longrightarrow C_6H_5SO_2OCH_3 + HCl$$
$$C_6H_5SO_2Cl + RNH_2 \longrightarrow C_6H_5SO_2NHR + HCl$$
$$C_6H_5SO_2Cl + R_2NH \longrightarrow C_6H_5SO_2NR_2 + HCl$$

The last two reactions are of importance as being the basis of the Hinsberg method of separating and characterizing amines. Obviously tertiary amines (R_3N) cannot react with the acid chloride. They may be separated by extraction or distillation after the primary and secondary amines have been converted into the substituted benzene sulfonamides, $C_6H_5SO_2NHR$ and $C_6H_5SO_2NR_2$. These two sulfonamides are readily separated by treating with an excess of sodium hydroxide. The sulfonamide obtained from the primary amine has a hydrogen atom on nitrogen; this hydrogen is sufficiently acidic, due to the influence of the sulfonyl group, to cause the compound to dissolve in sodium hydroxide. The other substance derived from the secondary amine contains no replaceable hydrogen, cannot form a salt, and does not dissolve.

$$\left.\begin{matrix} C_6H_5SO_2NR_2 \\ C_6H_5SO_2NHR \end{matrix}\right\} \xrightarrow{NaOH} \underset{\text{Insoluble, filter}}{C_6H_5SO_2NR_2} + \underset{\text{Soluble}}{C_6H_5SO_2NRNa}$$

$$C_6H_5SO_2NRNa \xrightarrow{HCl} C_6H_5SO_2NHR$$

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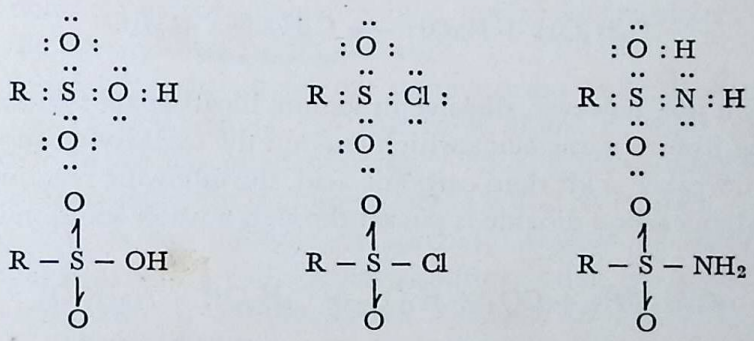
The sulfonamides on boiling with 25 per cent hydrochloric acid are hydrolyzed, regenerating the amines and sulfonic acid. Thus, after the two sulfonamides have been separated, as described, the amines are recovered by hydrolysis.

$$C_6H_5SO_2NHR \xrightarrow[HCl]{H_2O} C_6H_5SO_3H + RNH_2$$

$$C_6H_5SO_2NR_2 \xrightarrow[HCl]{H_2O} C_6H_5SO_3H + R_2NH$$

Structure of Sulfonyl Compounds. In the sulfonic acids, the sulfur atom is directly joined to carbon. The contrast between the sulfonic acids and the esters of sulfuric acid has been discussed in connection with the aliphatic sulfonic acids (p. 344).

The linkage between oxygen and sulfur in the sulfonic acids and their derivatives is, like the oxygen-sulfur linkage in the sulfoxides and sulfones (p. 346), a coordinate covalence. The electronic structures of a sulfonic acid, a sulfonyl chloride, and a sulfonamide are shown below, together with formulas using the convention we have adopted for representing a coordinate covalence.



(The electronic structure of the aryl group R is not written except for the one link joining the carbon atom to the sulfur.) It is probably not worth while to try to represent the special sulfur to oxygen linkage in these compounds every time the formula is written. With suitable mental reservations, such noncommittal formulas as $C_6H_5SO_2OH$, $C_6H_5SO_2Cl$, and $C_6H_5SO_2NH_2$ are sufficient.

PHENOLS

The hydroxy derivatives of aromatic hydrocarbons which have the OH group directly attached to the ring are called *phenols*. **Phenol,** or **carbolic acid,** C_6H_5OH, is the most important representative of the class. It is a colorless, crystalline substance which melts at 41°. Small amounts of water dissolved in phenol lower the melting point below room temperature.

The phenols which are derivatives of toluene are called *cresols*.

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The physical properties of these substances and phenol are listed below.

Name	*Formula*	*Boiling Point*	*Melting Point*	*Solubility Grams in 100 Grams of H_2O*
Phenol	C_6H_5OH	182°	41°	8 at 25° Miscible at 68°
o-Cresol	$CH_3C_6H_4OH(o)$	191°	31°	3 at 35°
m-Cresol	$CH_3C_6H_4OH(m)$	203°	10°	2.4 at 25°
p-Cresol	$CH_3C_6H_4OH(p)$	201°	35°	2.4 at 40°

As would be expected, the introduction of one OH group has made the substances somewhat soluble in water.

Reactions of Phenols. All the simple phenols (with the exception of the nitrophenols) are very weak acids but are sufficiently acidic to dissolve in sodium hydroxide.[1]

$$C_6H_5OH + NaOH \longrightarrow \underset{\text{Sodium phenoxide}}{C_6H_5ONa} + H_2O$$

They will not, however, dissolve in sodium bicarbonate solution, thus differing from organic acids which contain the carboxyl group. Since they are weaker acids than carbonic acid, the following reaction takes place when carbon dioxide is passed through a water solution of their salts.

$$C_6H_5ONa + CO_2 + H_2O \longrightarrow C_6H_5OH + NaHCO_3$$

The hydroxyl group in phenols is very different from that in alcohols. The acyl derivatives (the esters) cannot be made by direct esterification. They are prepared by the use of acid anhydrides or acid chlorides.

$$C_6H_5OH + (CH_3CO)_2O \longrightarrow \underset{\text{Phenyl acetate}}{C_6H_5OCOCH_3} + CH_3COOH$$

The aryl halides cannot be readily prepared from phenols either by the action of the phosphorus trihalides or by the action of halogen acids. With phosphorus pentachloride or bromide, however, phenols yield the corresponding halides, but in poor yields.

In general, phenols are to be contrasted with alcohols and also with acids. They form a separate class and are most closely related to the enols (p. 267). If we compare the Kekulé formula for phenol with

[1] The dissociation constant of phenol is about 1.7×10^{-10}. (Cf. p. 77.)

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the formula for an enol the analogy is evident; both compounds contain the grouping $-C = C(OH)-$. *The hydroxyl group directly attached to an unsaturated carbon atom is acidic.*

Phenol ethers are readily prepared by the action of an alkyl halide on the sodium salt of a phenol (sodium phenoxide).

$$C_6H_5ONa + C_2H_5Br \xrightarrow{\text{Heated}} C_6H_5OC_2H_5 + NaBr$$

Methyl sulfate may be used in place of methyl iodide in the preparation of the methyl ethers.

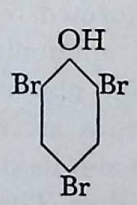
$$C_6H_5ONa + (CH_3)_2SO_4 \longrightarrow C_6H_5OCH_3 + CH_3OSO_2ONa$$

Phenols can be converted into the parent hydrocarbons by heating to a high temperature with zinc dust.

$$C_6H_5OH + Zn \xrightarrow{\text{Heat}} C_6H_6 + ZnO$$

When a solution of a phenol is treated with ferric chloride, an intense color is produced, which is blue, green, red, or violet depending on the other groups in the molecule.

The hydroxyl group in phenol orients ortho and para and also makes the replacement of the hydrogen atoms in those positions easier than in the parent hydrocarbon. Thus, if an aqueous solution of phenol is treated with bromine water, a white precipitate is at once formed; this is an unstable compound, tribromophenolbromide, $Br_4C_6H_2O$. On treating with sodium bisulfite solution, the extra halogen atom is removed and tribromophenol is formed (mp 96°). This compound, in which the halogen atoms are in the ortho and para positions, is known as 2,4,6-*tribromophenol*. It is used for the identification of phenol and in one of the processes whereby bromine is obtained from seawater.



Production of Phenol. For many years phenol was obtained solely from coal tar. In refining, this substance is found in the "middle oils" and is obtained from them by extraction with aqueous sodium hydroxide. During World War I enormous quantities of phenol were needed to make the explosive **trinitrophenol (picric acid)**, and to

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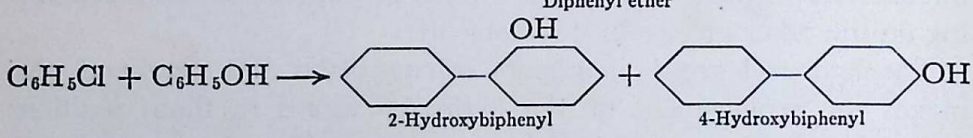
meet this demand synthetic phenol was produced. This synthetic method involves the preparation of sodium benzene sulfonate by the method previously described (p. 425). This salt is then fused with sodium hydroxide, and sodium phenoxide is formed. On dissolving the melt in water and acidifying, the phenol separates. It can then be purified by distillation. (The equations for the reactions involved in this process are given on pages 426 and 427.)

In more recent years, the demand for an abundant and cheap supply of phenol became so great that a new method of preparation from chlorobenzene was developed. Chlorobenzene is heated with dilute sodium hydroxide under very high pressure in a continuous tubular system of copper.

$$C_6H_5Cl + 2NaOH \longrightarrow C_6H_5ONa + NaCl + H_2O$$

At the same time some diphenyl ether and some 2-hydroxybiphenyl and 4-hydroxybiphenyl are formed.

$$C_6H_5ONa + C_6H_5OH \rightleftharpoons \underset{\text{Diphenyl ether}}{C_6H_5OC_6H_5} + NaOH$$



The reaction which furnishes diphenyl ether is, it will be noticed, reversible. Consequently, by adding diphenyl ether to the initial reaction mixture of chlorobenzene and sodium hydroxide, the formation of this byproduct can be suppressed.

Industrial Uses of Phenol. The increased demand for phenol is largely due to the growth of the synthetic resin industry. Synthetic resins are used in the manufacture of fountain pens, phonograph records, pipestems, and as an insulator in electrical equipment. **Bakelite** is a synthetic resin formed by the action of formaldehyde on phenol in the presence of ammonia. This industry requires not only large amounts of phenol but also of formaldehyde. (Bakelite and other phenol-formaldehyde resins are discussed later in Chap. 26.) Great quantities of phenol are also used in the manufacture of drugs, photographic developers, and dyes. Phenol itself is an excellent antiseptic, and dilute water solutions of phenol (usually called *carbolic acid*) are widely used for this purpose.

In 1924, 10,500,000 lb of phenol were produced in the United States; in 1940 some 96,000,000 lb were produced, of which about 75 per cent was prepared by synthetic methods.

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Phenol Ethers. The preparation of phenol ethers by the alkylation of phenol has already been discussed. Diphenyl ether, $C_6H_5OC_6H_5$ (bp 259°), a byproduct in the manufacture of phenol from chlorobenzene, can be prepared by heating phenol with a dehydrating agent such as zinc chloride or by the action of bromobenzene on potassium phenoxide. Finely divided metallic copper is an essential catalyst for this reaction.

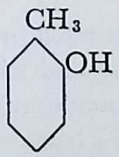
$$C_6H_5OK + BrC_6H_5 \xrightarrow[210°]{Cu} C_6H_5OC_6H_5$$

Diphenyl ether is used as a high-temperature heat transfer medium.

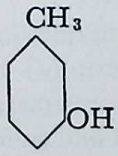
The most important phenyl ethers are **anisole,** $C_6H_5OCH_3$, a liquid which boils at 154°, and **phenetole,** $C_6H_5OC_2H_5$, which boils at 172°. They are neutral substances insoluble in water. When heated with aluminum chloride or boiled with hydrobromic or hydriodic acid, the phenol ethers are cleaved with the regeneration of the phenol.

$$C_6H_5OCH_3 + HI \longrightarrow C_6H_5OH + CH_3I$$

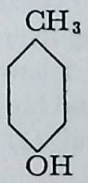
Hydroxyl Derivatives of Alkyl Benzenes. The hydroxyl derivatives of toluene are the **cresols.** Their physical properties are given in the table on page 430.



Ortho cresol
or
2-hydroxytoluene



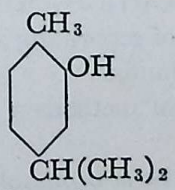
Meta cresol
or
3-hydroxytoluene



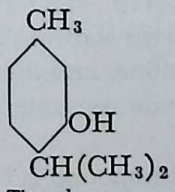
Para cresol
or
4-hydroxytoluene

They are recovered from coal tar and used as antiseptics and, to some extent, in the preparation of other aromatic compounds.

Thymol and **carvacrol** are two hydroxyl derivatives of para cymene (p. 417) which occur in many essential oils.



Carvacrol



Thymol

Thymol melts at 51° and boils at 232°; carvacrol is a liquid at room

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temperature (mp + 0.5) and boils at 237°. Both compounds resemble phenol in their chemical reactions. Thymol is used in medicinal preparations as an antiseptic. It is much less poisonous than phenol.

The general method for synthesizing the hydroxyl derivatives of the alkyl benzenes is by reduction of the corresponding hydroxy ketones. The reaction used for this purpose is known as the *Clemmensen reduction* and is described on page 492.

QUESTIONS AND PROBLEMS

1. Write structural formulas for *p*-chlorophenol, meta benzenedisulfonic acid, para iodotoluene, benzyl chloride, *p*-bromobenzenesulfonic acid, *p*-toluenesulfonamide, and meta cresol.

2. Compare by means of equations the behavior of phenol and *n*-hexanol toward the following reagents: (*a*) NaOH; (*b*) H_2SO_4; (*c*) HBr; (*d*) CH_3COOH and a small amount of sulfuric acid; (*e*) $(CH_3CO)_2O$.

3. How would you prepare the following substances starting with any of the coal tar crudes: (*a*) iodobenzene; (*b*) benzyl chloride; (*c*) *p*-nitrotoluene; (*d*) *p*-bromotoluene; (*e*) *m*-bromobenzenesulfonic acid?

4. Compare the structural formulas and chemical reactivity of bromo benzene, allyl bromide, benzyl bromide, and vinyl bromide.

5. State briefly the rules describing the positions taken by substituents introduced into benzene derivatives.

6. Applying the rules stated in question 5, predict what products will be formed in the following reactions: (*a*) ethylbenzene and nitric acid, (*b*) ethylbenzene and bromine in the presence of ferric bromide, (*c*) nitrobenzene and sulfuric acid, (*d*) para cresol and sulfuric acid, (*e*) benzenesulfonic acid and bromine.

7. Write structural formulas for benzenesulfonic acid, benzenesulfonyl chloride, and benzenesulfonamide. Compare these formulas with those of butanesulfonic acid and its chloride and amide.

8. Describe two industrial methods of synthesizing phenol and explain why phenol is of such importance in the chemical industry.

9. What chemical tests would you use to distinguish between $CH_3C_6H_4OCH_3$, $C_2H_5C_6H_4OH$, and $CH_3C_6H_4CH_2OH$?

10. Write equations showing a method of separating a mixture of hexylamine, ethylbutylamine, and dimethylbutylamine.

11. How could you separate by chemical methods a mixture of phenol and *n*-valeric acid?

12. An organic compound is believed to be *m*-bromophenol. Indicate the chemical reactions you would use to prove that the compound does have that structure, and then outline a synthesis of the compound from benzene.

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13. Compare the properties, preparation, and importance of the aliphatic and aromatic sulfonic acids.

14. Contrast the chemical properties of: (*a*) $C_6H_5SO_2NH_2$ and $C_6H_5CONH_2$, (*b*) phenol and acetoacetic ester, (*c*) chlorobenzene and benzyl chloride.

15. Complete the reactions: (*a*) $CH_3C_6H_4SO_3H + PCl_5$, (*b*) $C_6H_5ONa + (C_2H_5)_2SO_4$, (*c*) $HOC_6H_4SO_3H + (CH_3CO)_2O$, (*d*) $CH_3C_6H_5 + HNO_3 + I_2$, (*e*) $CH_3C_6H_4Br$ + Mg in ether.

16. Indicate the steps for the conversions: (*a*) benzene to anisole, (*b*) toluene to the methyl ester of *p*-toluenesulfonic acid, (*c*) benzene to diphenyl ether, (*d*) *p*-cymene to carvacrol, (*e*) *p*-hydroxybenzenesulfonic acid to phenol.

17. Predict the major product expected from sulfonating each of the following: (*a*) thymol, (*b*) meta cresol, (*c*) meta xylene, (*d*) diphenyl ether.

18. What reactions would you employ to prove the structure of thymol?

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Chapter 23

AROMATIC NITRO COMPOUNDS, AMINES, DIAZONIUM SALTS, AND AZO DYES

The Nitration of Aromatic Compounds. The hydrogen atoms which are attached to the aromatic ring are readily replaced by the nitro group. This is one of the characteristic reactions of aromatic compounds. The nitration is usually carried out by treating the substance with a mixture of concentrated nitric and sulfuric acids. The sulfuric acid itself does not react, but provides the experimental conditions under which the nitric acid is most effective. Some compounds like phenol are nitrated even by dilute nitric acid.

The **nitro compounds** are quite distinct from the esters of nitrous acid. A comparison of the structural formulas of **nitrobenzene** (formed by the nitration of benzene), $C_6H_5 - NO_2$, and ethyl nitrite, $C_2H_5 - O - N = O$, makes this evident. In the nitro compounds there is a carbon to nitrogen linkage. Unlike esters, *nitro compounds are not hydrolyzed.*

Importance of Nitro Compounds. Aromatic nitro compounds are of importance because of their use as explosives, and because they may be readily reduced to the corresponding **primary amines.** These in turn are the starting materials for the manufacture of many dyes. The presence of one or more nitro groups in an aromatic nucleus markedly influences the chemical properties of other atoms or groups in the molecule; this is particularly true if the groups are in the ortho and para positions. The nitro group is almost unique in the extent of this influence which it exerts. For this reason we shall often have occasion to refer to the special properties of nitro phenols, nitro amines, and nitro halogen compounds.

The Products of the Nitration of Benzene and Toluene. The chief products which may be obtained by the nitration of benzene and toluene are listed on the following page; they are all insoluble in water.

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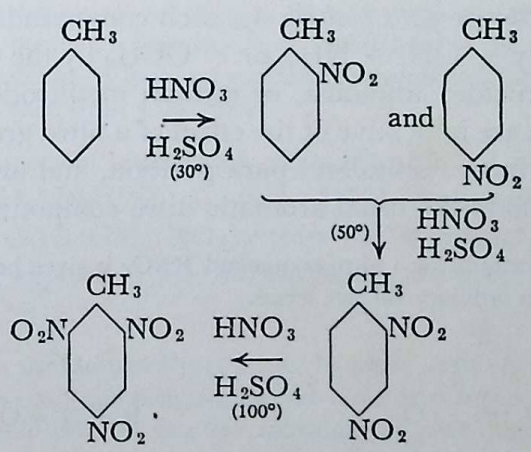
Name	*Formula*	*Boiling Point*	*Melting Point*
Nitrobenzene	$C_6H_5NO_2$	211°	+ 6°
m-Dinitrobenzene	$C_6H_4(NO_2)_2(m)$	302°	90°
o-Nitrotoluene	$CH_3C_6H_4NO_2(o)$	222°	−11°
p-Nitrotoluene	$CH_3C_6H_4NO_2(p)$	238°	51°
m-Nitrotoluene (obtained in small amounts in the mono-nitration)	$CH_3C_6H_4NO_2(m)$	231°	16°
2,4-Dinitrotoluene	$CH_3C_6H_3(NO_2)_2$	300°	70°
2,4,6-Trinitrotoluene (TNT)	$CH_3C_6H_2(NO_2)_3$	—	81°

Nitrobenzene is a slightly yellow liquid with a characteristic odor somewhat reminiscent of almonds. It is prepared on a very large scale chiefly for use in the preparation of aniline. The nitration of benzene is accomplished by agitating a mixture of the hydrocarbon with sulfuric and nitric acids. The product is insoluble in the nitrating mixture and may be readily separated. It is purified by washing with water and then distilling.

The introduction of a second nitro group into benezene is more difficult than the introduction of the first. This fact illustrates the general rule that the presence of a meta-orienting group makes substitution more difficult than in benzene itself. In order to prepare **meta dinitrobenzene,** a higher temperature is required and fuming nitric acid is employed. The introduction of a third nitro group into benzene is very difficult.

Toluene may be nitrated in a stepwise manner to 2,4,6-trinitrotoluene.



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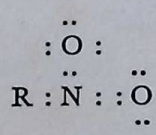
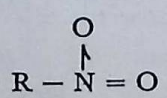
Since toluene contains the methyl group which orients ortho and para, its nitration is more readily accomplished than is the nitration of benzene. This contrast is particularly evident in the formation of the 2,4,6-trinitrotoluene without difficulty. The nitration is done in three stages, each at a somewhat higher temperature than its predecessor; and the spent acid from the trinitration is used for the dinitration, and so on.

Aromatic Nitro Compounds as High Explosives. Trinitrotoluene, usually called **TNT,** was prepared in enormous quantities during both World Wars and was used in shells as a high explosive. It is relatively insensitive to shock and can, therefore, be used in filling projectiles which are fired from guns and which could not contain the more sensitive nitrates of cellulose (p. 297). It is detonated by means of a special charge called a *booster* (p. 449), which is ignited by a time fuse or on impact. The explosion of aromatic nitro compounds, like that of glycerine trinitrate, is a rapid combustion in which the oxygen comes from *within* the molecule itself. Because the nitro groups supply this oxygen, the explosive force increases with the number of nitro groups. Although trinitrobenzene is an excellent explosive, it is so difficult to introduce the third nitro group into benzene that the manufacture is out of the question. A military high explosive is made from benzene by first preparing phenol (p. 432), which is then nitrated to picric acid (**PA**). This differs from TNT only in having an hydroxyl group in place of a methyl.

Structure of Nitro Compounds. The fact that nitro compounds contain a nitrogen to carbon linkage is established by their reduction to primary amines (RNH_2). The isomeric nitrites do not yield any reduction product in which a nitrogen atom is thus attached. The fact that nitro compounds are not hydrolyzed has already been emphasized. The carbon to nitrogen linkage in both the aliphatic and aromatic nitro compounds is firm. The *only exception* to this statement is the behavior of polynitro compounds which contain *two nitro groups* in the *ortho* or *para position.* In such compounds *one nitro group may be replaced* by $-OH$, $-NH_2$, or $-OCH_3$ by the vigorous action of sodium hydroxide, ammonia, or sodium methoxide, respectively. These reactions are indicative of the effect of a nitro group on another atom or group in the ortho and para position, and are not to be regarded as typical of the usual aromatic nitro compounds.

The electronic formula for a nitro compound RNO_2 is given below together with its representation in ordinary valence terms.





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There is, of course, no real distinction between the two oxygen atoms; the nitro group, like the carboxyl ion, exhibits resonance. For most purposes the noncommittal formula, RNO_2, is adequate. The electronic structure of the nitroso compounds (p. 452), R — N = O, corresponds to an orthodox double linkage.

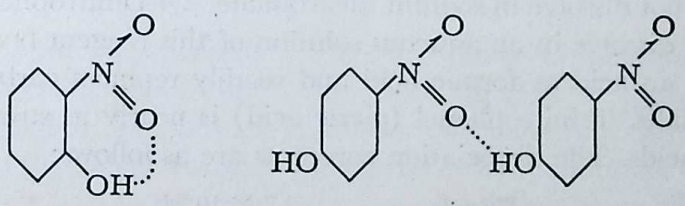
$$R : \ddot{N} : : \ddot{\underset{\cdot\cdot}{O}}$$

The relation between a nitroso compound and a nitro compound is very similar to that between an amine and an amine oxide (p. 194).

NITROPHENOLS

Nitration of Phenol. The ortho and para nitrophenols may be prepared by the nitration of phenol with dilute nitric acid. The fact that dilute acid may be employed is another illustration of the accelerating influence of a group of Class I (p. 423) on substitution reactions. The isomers are separated by steam distillation. The **ortho nitrophenol** is volatile with steam and intensely yellow; it melts at 45°. The **para nitrophenol** melts at 114° and is not volatile with steam.

This difference in volatility between the ortho and para nitrophenols is ascribed to the hydrogen bonding or chelation (p. 83) in the ortho compound. The para isomer, which has a normal hydroxyl group, undergoes intermolecular association like the alcohols and acids; it is, therefore, less volatile and higher boiling than the ortho compound. Consequently, the ortho and para nitrophenols, by contrast with



such isomers as the ortho and para xylenes, are easily separated by distillation. The effect of hydrogen bonding is also seen in the solubilities of the nitrophenols. The ortho isomer is less soluble in hydroxyl containing solvents and more soluble in non-hydroxylic solvents than is the para isomer.

Further nitration of ortho and para nitrophenol yields **2,4-dinitrophenol,** $C_6H_3(OH)(NO_2)_2$ (mp 112°), and eventually 2,4,6-trinitrophenol, $C_6H_2(OH)(NO_2)_3$ (mp 123°), **picric acid (PA),** an important high explosive. The nitrophenols are only slightly soluble in water.

Picric Acid. In the industrial preparation of picric acid, phenol is dissolved in concentrated sulfuric acid and then treated with nitric acid, first at 0° and then 100°. The process probably involves first the formation of para phenol sulfonic acid,

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$C_6H_4(OH)SO_3H$, and then the replacement by the nitro group of both the sulfonic acid group and the ortho hydrogen atom, yielding 2,4-dinitrophenol. The final nitration at 100° introduces the third nitro group.

The solutions of picric acid are intensely yellow, and wool and silk may be dyed by immersion. The salts of picric acid with the heavy metals (the picrates) are sensitive explosives when dry and easily detonate when subjected to mechanical shock. Picric acid itself, however, like TNT, is not sensitive and can be used in filling shells. Picric acid is often used in the laboratory in the isolation of bases since its salts with organic bases are often but slightly soluble and usually nicely crystalline. Picric acid forms loose molecular addition compounds with many aromatic hydrocarbons, particularly those containing a number of rings. These crystalline **molecular compounds** are sometimes useful in separating the complex aromatic hydrocarbons.

Sulfur Dyes. Picric acid will color wool and silk but it is not of importance as a dye. From it, however, by heating with sodium polysulfide solution is obtained the important dye **sulfur black.** (The United States production of this dye in 1940 exceeded 14,000,000 lb.) The structure of sulfur black, which can also be prepared from 2,4-dinitrophenol and sodium sulfide, is not known.

Sulfur black is the most important member of the group of sulfur dyes prepared by heating various aromatic nitrophenols, aminophenols, or amines with sodium polysulfide. The sulfur dyes are usually applied by dissolving them in sodium sulfide solution and dyeing the cloth in this solution. They are used with cotton.

The Acidic Properties of the Nitrophenols. The remarkable influence of the nitro group is strikingly shown by a comparison of the acidic properties of phenol and its nitro derivatives.

Phenol and most of its simple derivatives are such weak acids that they will not dissolve in sodium bicarbonate. 2,4-Dinitrophenol, however, will dissolve in an aqueous solution of this reagent because it is as strong an acid as formic acid and readily replaces carbonic acid from its salts. Trinitrophenol (picric acid) is nearly as strong as the mineral acids. The dissociation constants are as follows:

Phenol	1.7×10^{-10}
p-Nitrophenol	6.4×10^{-8}
2,4-Dinitrophenol	1.0×10^{-4}
Picric acid	1.6×10^{-1}

The dissociation constants of carbonic acid are: $H_2CO_3 \rightleftharpoons HCO_3^- + H^+$, 1×10^{-7} and $HCO_3^- \rightleftharpoons CO_3^= + H^+$, 5×10^{-11} (p. 77). Many phenols may be separated from acids and nitrophenols by the difference in solubility in sodium bicarbonate solution. The solubility of an acid in a given alkaline solution (with the formation of a salt) depends on two factors: (1) the strength of the acid group and (2) the solubility. Phenols of high molecular weight are often only very slightly soluble and will not dissolve even in dilute sodium hydroxide. Similar considerations apply to acids. However, as a general rule, acids of low molecular weight may be extracted from an ether solution by sodium bicarbonate or sodium carbonate while phenols require sodium hydroxide. The nitrophenols, however, are often extracted by sodium

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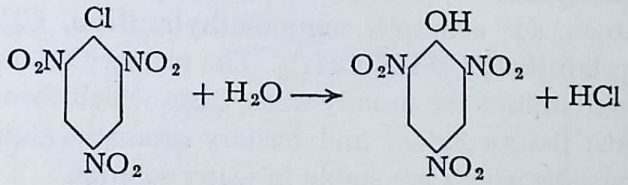
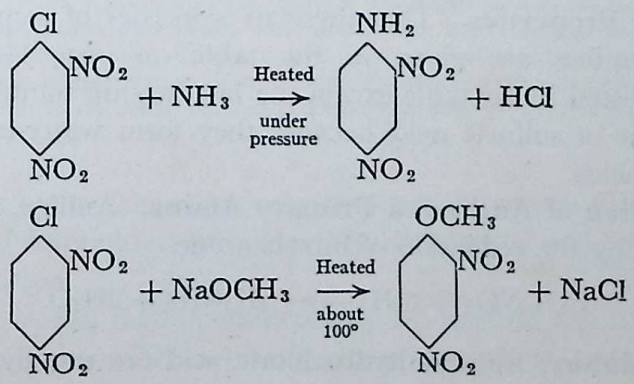
carbonate since they are stronger acids if the nitro groups are in the ortho or para position to the hydroxyl. Like the phenols, many highly enolic substances are soluble in dilute sodium hydroxide and may be extracted by this reagent.

Reactivity of Nitro Aryl Halides. We have just seen the marked effect of a nitro group in the ortho or para position on the acidity of a phenol. The nitro group modifies the molecule so that the hydroxyl group is more acidic. The influence of the nitro group is not confined to a hydroxyl group, but also extends to a halogen atom in the ortho or para position. Here, the effect of the nitro group is to make the halogen atom much more readily replaced by such groups as OH, NH_2, and OCH_3. The simple aryl halides (e.g., C_6H_5Cl), like the vinyl halides, are extremely unreactive. The introduction of a nitro group in the ortho or para position, however, makes the halogen atom of an aryl halide sufficiently reactive so that it may be readily replaced by many groups. The effect is cumulative and the chlorine atom in 2,4,6-trinitrochlorobenzene (picryl chloride) is replaced by hydroxyl when the compound is boiled with water alone.



The mononitro compounds (ortho and para nitrochlorobenzene) must be heated above 100° with *sodium hydroxide* to bring about a similar reaction. The nitro aryl halides (with the nitro groups ortho or para to the halogen atom) will also react with ammonia or sodium methoxide, yielding an amine or a phenolic ether. As an illustration, the behavior of 2,4-dinitrochlorobenzene may be cited.



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Nitrophenols from Chlorobenzene. The enhanced reactivity of the halogen atom in certain of the nitro aryl halides is utilized in the preparation of the nitrophenols. The direct nitration of phenol with the formation of the ortho and para derivatives is troublesome, because phenol is easily oxidized by nitric acid. This difficulty may be avoided by starting with chlorobenzene and proceeding to the nitrophenols through the nitrochlorobenzenes. The steps in the entire synthesis are as follows:

$$C_6H_5Cl \xrightarrow[H_2SO_4]{HNO_3} \underset{\text{o- and p-Isomers separated}}{C_6H_4Cl(NO_2)} \xrightarrow[\text{And subsequent acidification}]{NaOH\ 100^\circ} NO_2C_6H_4OH.$$

AROMATIC AMINES

Classification. The aromatic amines, like the aliphatic amines, are divided into three classes: (1) **primary amines,** (2) **secondary amines,** and (3) **tertiary amines.** As an example of each class we may mention: (1) **aniline,** $C_6H_5NH_2$, (2) **diphenylamine,** $(C_6H_5)_2NH$, and (3) **triphenylamine,** $(C_6H_5)_3N$. Mixed aliphatic-aromatic amines are also known; for example, **monomethylaniline,** $C_6H_5NHCH_3$, and **dimethylaniline,** $C_6H_5N(CH_3)_2$. The primary aromatic amines and the mixed amines are usually weak bases which form salts with mineral acids; the secondary and tertiary aromatic amines are too weak to form salts which are stable in water solution.

The primary amines are by far the most important since they may be readily prepared by reducing aromatic nitro compounds and can be converted into many useful products, particularly dyes. Indeed, the name of the commonest primary amine, *aniline*, has become so associated with the synthetic dye industry that the term *aniline dyes* is often used synonymously with *coal-tar dyes*, and covers many compounds which have no connection whatsoever with aniline.

Physical Properties. The physical properties of some common aromatic amines are given in the table on page 443. All the substances listed in the table except the last two are soluble in dilute hydrochloric or sulfuric acid because they form water-soluble salts with these acids.

Preparation of Aniline, a Primary Amine. Aniline, $C_6H_5NH_2$, is prepared by the reduction of nitrobenzene.

$$C_6H_5NO_2 + 6[H] \longrightarrow C_6H_5NH_2 + 2H_2O$$

In the laboratory, tin and hydrochloric acid are usually employed;

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Name	*Formula*	*Boiling Point*	*Melting Point*	*Solubility Grams per 100 Grams of Water*
Aniline	$C_6H_5NH_2$	184°	− 6°	3.5 at 25°
o-Toluidine	$CH_3C_6H_4NH_2$	201°	−21°	1.5 at 25°
m-Toluidine	$CH_3C_6H_4NH_2$	203°	−32°	Slightly soluble
p-Toluidine	$CH_3C_6H_4NH_2$	201°	+44°	0.730 at 21°
Monomethylaniline	$C_6H_5NHCH_3$	196°	−57°	Very slightly soluble
Dimethylaniline	$C_6H_5N(CH_3)_2$	194°	+ 2°	Very slightly soluble
Diphenyl amine	$(C_6H_5)_2NH$	302°	53°	Insoluble
Triphenyl amine	$(C_6H_5)_3N$	365°	127°	Insoluble

industrially, the cheaper scrap iron replaces the tin and only a little acid is employed. The industrial process, thus, is essentially the reduction of nitrobenzene by iron and water, the products being aniline

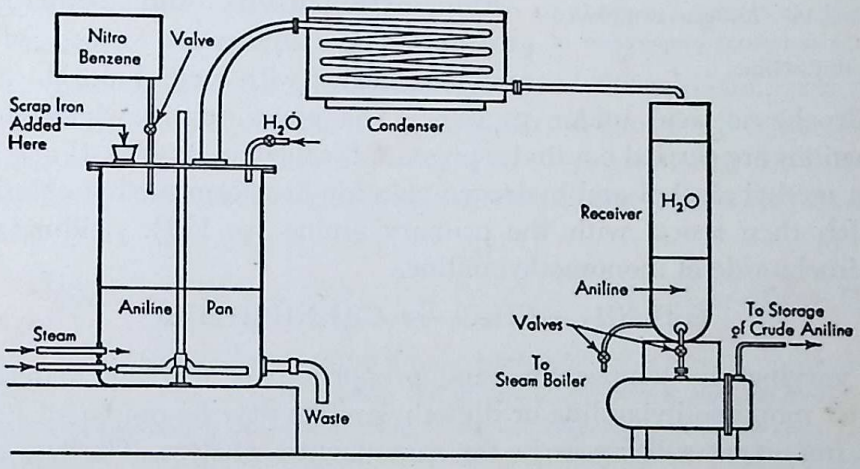

FIG. 15. Diagram illustrating the essential equipment used in the industrial preparation of aniline. The nitrobenzene, water and a little acid are first introduced into the reaction vessel. Scrap iron is dropped in through a man-hole and the mixture stirred. After the reduction is complete, steam is introduced; the vapors are condensed and the distillate allowed to settle in tall tanks. The crude aniline is drawn off; the water goes to the steam generator.

and ferric hydroxide; these are separated by steam distillation (Fig. 15). Nitro compounds are smoothly reduced to amines by catalytic hydrogenation.

Aniline is also made commercially by heating chlorobenzene and ammonia at about 200° with a mixture of cuprous oxide and cuprous

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chloride. The latter is a catalyst while the cuprous oxide participates in the reaction.

$$2C_6H_5Cl + 2NH_3 + Cu_2O \xrightarrow{Cu_2Cl_2} 2C_6H_5NH_2 + Cu_2Cl_2 + H_2O$$

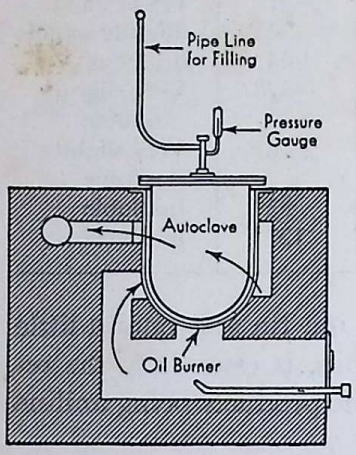

FIG. 16. Autoclave employed in the industrial preparation of dimethylaniline.

The recovered cuprous chloride is treated with alkali to convert most of it to the oxide, and the mixture is then used for the next charge.

The **toluidines,** $CH_3C_6H_4NH_2$, are prepared by the nitration of toluene and the reduction of the products. Like aniline they are important dye intermediates. The ortho and para compounds are most readily obtained since the nitration of toluene yields chiefly the ortho and para nitrotoluenes.

Monomethylaniline and Dimethylaniline. These amines are formed when aniline is heated with methyl alcohol and hydrochloric acid under pressure. The apparatus in which such reactions are carried out under pressure is called an *autoclave* (Fig. 16). The methyl alcohol and hydrogen chloride first form methyl chloride which then reacts with the primary amine (p. 188), yielding the hydrochloride of monomethylaniline.

$$C_6H_5NH_2 + CH_3Cl \longrightarrow C_6H_5NHCH_3{\cdot}HCl$$

By varying the temperature and proportions of reacting materials either monomethylaniline or dimethylaniline may be prepared. Both are important substances in the manufacture of dyes. The latter is the starting material for the preparation of the military explosive, tetryl (p. 449).

Aromatic Amines Are Weak Bases. The weak basic strength of aniline and its two derivatives is shown by the following basic dissociation constants.

Aniline	$K_B = 3.5 \times 10^{-10}$
Methylaniline	$K_B = 2.6 \times 10^{-10}$
Dimethylaniline	$K_B = 2.4 \times 10^{-10}$

It will be recalled that ammonia has the value 2×10^{-5} and the aliphatic amines about 5×10^{-4} (p. 188).

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Reaction with Nitrous Acid. Primary, secondary, and tertiary amines differ in their reaction with nitrous acid. This may be illustrated by comparing the action of this reagent with aniline, monomethylaniline, and dimethylaniline. With the first, a water-soluble **diazonium salt,** $C_6H_5N_2Cl$, is formed. This compound will be further considered shortly.

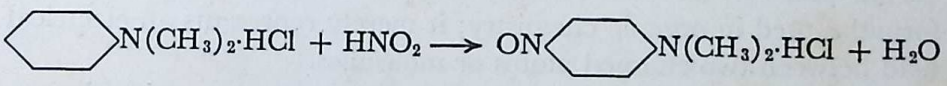
$$C_6H_5NH_3Cl + HNO_2 \longrightarrow C_6H_5\underset{\underset{N}{|||}}{N} - Cl + 2H_2O$$

With monomethylaniline, a yellow, oily **nitroso compound** is produced.

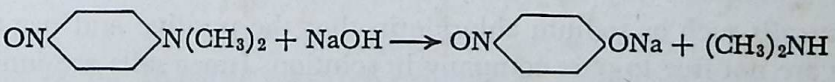
$$C_6H_5NHCH_3{\cdot}HCl + HNO_2 \longrightarrow C_6H_5\underset{\underset{NO}{|}}{N}CH_3 + HCl + H_2O$$

This substance is such a weak base that it will not dissolve in aqueous acid solutions. When treated with alcoholic hydrogen chloride, the nitroso group migrates from the nitrogen to the para position of the nucleus.

The para hydrogen atom in the nucleus of dimethylaniline is unusually reactive and is replaced by the **nitroso group** when the compound is treated with dilute nitrous acid. The product is the hydrochloride of ***p*-nitrosodimethylaniline** which is a yellow, crystalline solid.

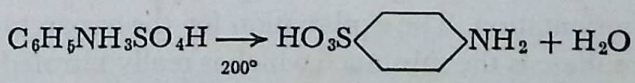


The nitroso group, like the nitro group, profoundly effects an atom or group attached to the ortho or para position of the aromatic nucleus. For this reason, *p*-nitrosodimethylaniline, on boiling with alkali, decomposes forming dimethylamine and the salt of the corresponding hydroxyl compound (nitroso phenol).



This is probably the best method of preparing pure dimethylamine.

Sulfanilic Acid. Aniline may be sulfonated, producing the para sulfonic acid. The amine is first neutralized with concentrated sulfuric acid, forming the solid **aniline acid sulfate,** $C_6H_5NH_3SO_4H$. This, on baking in an oven at 200°, forms sulfanilic acid and water.



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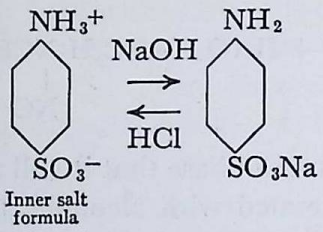
Sulfanilic acid is a solid only slightly soluble in organic solvents and in water. It is nonvolatile and has no definite melting point; in these respects it resembles an inorganic salt rather than an organic compound. It is soluble in sodium carbonate or sodium hydroxide, forming a sodium salt; acidification precipitates sulfanilic acid. It has such weak basic properties that it does not dissolve even in concentrated hydrochloric acid.

Inner Salt Formula for Sulfanilic Acid. All the facts mentioned in the last paragraph are best represented by the inner salt formula already encountered in amino acids (Chap. 19).



This formula is written to indicate that an internal neutralization has occurred. In this process the acid hydrogen of the sulfonic acid group has added to the NH_2 group. The "linkage" between the NH_3^+ group and the SO_3^- group is of the sort which we meet in inorganic salts such as sodium chloride and ammonium sulfate. This linkage we are quite certain is not a linkage in the sense of the ordinary valence formulas used in organic chemistry; it merely represents an electrical field between two charged atoms or molecules.

In the inner salts, we imagine that the positive and negative charges are localized on particular groups of the large molecule. The simple formula, $NH_2C_6H_4SO_3H$, is often written for sulfanilic acid, but the representation, $NH_3^+C_6H_4SO_3^-$, is to be preferred. Inner salts differ from salts such as sodium chloride in that the positive and negative ions are not free to part company in solution. Inner salts are ionized but not dissociated.

Nitration of Aniline. When aniline is nitrated in the usual way with a mixture of nitric and sulfuric acids there is a great deal of oxidation, but at a low temperature it is possible to obtain considerable amounts of the nitration product, which is **meta nitroaniline,** $C_6H_4NH_2(NO_2)$. At first sight this might appear to be contrary to the rules of orientation. The explanation for the apparent anomaly is that aniline sulfate is the substance which is really nitrated in the acid

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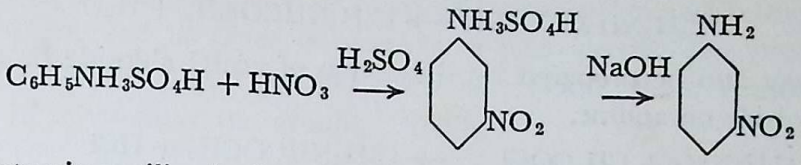
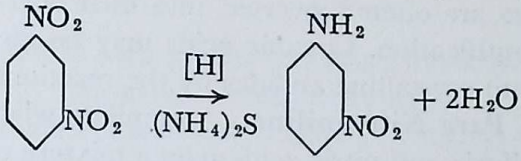
mixture, and that the $-NH_3^+$ group directs the incoming group into the meta position.

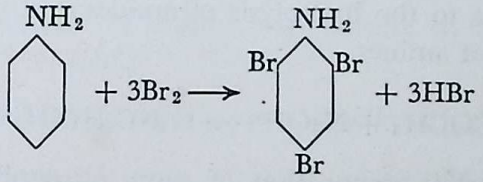


Meta nitroaniline is also prepared from meta dinitrobenzene which in turn can be readily prepared by the nitration of benzene. The reduction of one nitro group only is accomplished by heating the dinitro compound with ammonium sulfide. This rather unusual reagent is only effective in reducing groups which are very easily reduced.



The **ortho** and **para nitroanilines** (nitranilines) are prepared industrially by an indirect method described on page 448.

Tribromoaniline. Although the nitration of aniline appears abnormal, aniline is very similar to phenol in most substitution reactions. For example, on treating aniline with dilute bromine water a white precipitate of **2,4,6-tribromoaniline,** $Br_3C_6H_2NH_2$, is at once formed.



Acetanilide, $C_6H_5NHCOCH_3$, is the acetyl derivative of aniline. It is a substance of considerable importance both as an intermediate in the preparation of organic compounds and as a drug. It is one of the oldest of the so-called coal-tar medicinals. It has an effect on the human system which causes the lowering of the temperature of a patient suffering with fever. A substance which has this action is said to be an *antipyretic* or *febrifuge*. Acetanilide has been used less extensively in recent years for this purpose because more efficient and relatively less harmful drugs have been synthesized (e.g., phenacetin, p. 474).

The usual method of preparing acetanilide is exactly analogous to the preparation of acetamide from ammonium acetate.

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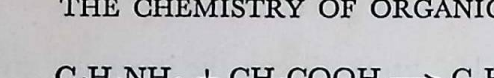
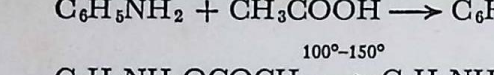
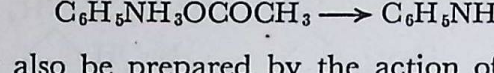


$$C_6H_5NH_2 + CH_3COOH \longrightarrow C_6H_5NH_3OCOCH_3$$

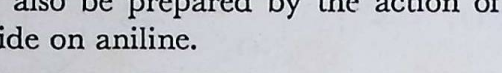


$$C_6H_5NH_3OCOCH_3 \xrightarrow{100°-150°} C_6H_5NHCOCH_3 + H_2O$$

It may also be prepared by the action of acetyl chloride or acetic anhydride on aniline.



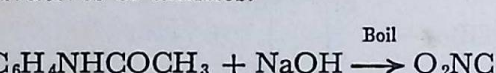
$$C_6H_5NH_2 + CH_3COCl \longrightarrow C_6H_5NHCOCH_3 + HCl$$



$$C_6H_5NH_2 + (CH_3CO)_2O \longrightarrow C_6H_5NHCOCH_3 + CH_3COOH$$

Acetanilide is a white crystalline solid which melts at 114°. It has no basic properties. In general, the acyl derivatives of the aromatic amines are crystalline solids which are easily purified. For this reason aromatic amines are often converted into their acyl compounds for purposes of identification. Organic acids may be identified by converting them into crystalline anilides by the reactions given above.

Synthesis of Para Nitroaniline. Acetanilide when nitrated with a mixture of sulfuric and nitric acids gives a mixture of the ortho and para nitro compounds; under special conditions the para isomer is the chief product. This affords a very convenient method of preparing para nitroaniline (para nitraniline), which, as we have seen above, is not the product of the direct nitration of aniline under the usual conditions. **Para nitroacetanilide** on boiling with sodium hydroxide is hydrolyzed, forming ***p*-nitroaniline** and sodium acetate. The reaction is analogous to the hydrolysis of amides and is general for the acyl derivatives of amines.



$$O_2NC_6H_4NHCOCH_3 + NaOH \xrightarrow{\text{Boil}} O_2NC_6H_4NH_2 + CH_3COONa$$

In the industrial preparation of para nitroaniline, the sodium acetate is converted into acetic acid which is used for preparing more acetanilide from aniline. Thus, the whole process may be considered as an *indirect nitration of aniline;* in order to get the proper orientation, a group is temporarily tied to the molecule and after it has served its purpose is removed. The acetyl group also protects the molecule from the oxidation which occurs when aniline itself is nitrated.

Nitroanilines as Dye Intermediates. The nitroanilines are widely used in the dye industry; they are all solids insoluble in water but soluble in dilute mineral acids because of their weak basic properties. Their melting points are: ortho 72°, meta 112°, para 148°.

Tetryl. A Nitramine. The nitroanilines which we have been discussing contain nitro groups attached to the ring carbon atoms. When

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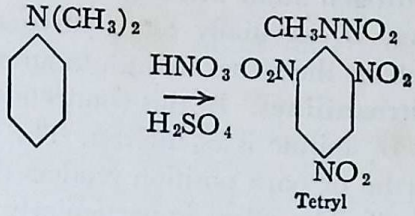
dimethylaniline is treated with a mixture of nitric and sulfuric acids, three nitro groups enter the ring in the ortho and para positions; in addition, one methyl group on nitrogen is oxidized to carbon dioxide and water, and its place is taken by a nitro group. The product, methyl-2,4,6-trinitrophenylnitramine, or **tetryl,** is a nitramine; that is, it contains the group $>NNO_2$.



Tetryl

Tetryl is a military high explosive of great importance. It is powerful, but too easily detonated for extensive use as a main filling. Its principal use, therefore, is a *booster;* a charge which is easily detonated by a detonator, such as mercuric fulminate or lead azide, and which is capable in turn of causing the detonation of a high explosive such as TNT. Another nitramine which is a powerful explosive is cyclonite or RDX (p. 150).

Neutral Aromatic Amines. Diphenylamine, $(C_6H_5)_2NH$, and **triphenylamine,** $(C_6H_5)_3N$, are representatives of the aryl secondary and tertiary amines. Diphenylamine is prepared by heating an equimolecular mixture of aniline and aniline hydrochloride in an autoclave at 200° to 230°.

$$C_6H_5NH_3Cl + C_6H_5NH_2 \longrightarrow C_6H_5NHC_6H_5 + NH_4Cl$$

It is used in the manufacture of certain dyes and is frequently incorporated into nitrocellulose products in which it prevents spontaneous decomposition. The triphenylamine is prepared by heating a mixture of diphenylamine, iodobenzene, potassium carbonate, and copper powder. The catalytic effect of the copper is similar to its action in promoting the formation of diaryl ethers (p. 433).

The most interesting fact about the di- and tri-aryl amines is the almost entire absence of basic properties. Thus, diphenylamine is so weak a base that it will dissolve in only the most concentrated acids. Triphenylamine has no basic properties. We have pointed out earlier that the introduction of an acyl group into ammonia produced a neutral substance—an amide ($RCONH_2$). We now see that two phenyl groups produce the same effect. If we were to examine the

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compound produced by the action of nitrous acid on monomethylaniline, $C_6H_5N(NO)CH_3$ (p. 445), we should find that this also was devoid of basic properties. The replacement of the hydrogen atom on the basic group by $-NO$ destroys the basic properties of monomethylaniline. We thus recognize that certain groups, such as the acyl group, the phenyl group, and the nitroso group, markedly affect the basicity of the nitrogen atom when they are attached to it. The alkyl group, however, is essentially like hydrogen since the alkyl amines are bases of about the same strength as ammonia.

Basicity of the Nitroanilines. In this connection, the behavior of the nitro derivatives of aniline is of interest. The introduction of a nitro group in the ortho or para position renders the compound less basic than aniline itself. The effect is particularly striking in 2,4,6-trinitroaniline, $(NO_2)_3C_6H_2NH_2$, which has no basic properties at all. This compound is related to picric acid as acetamide is to acetic acid and is often called *picramide*. Like other amides, but unlike aryl amines, it can be hydrolyzed by boiling with sodium hydroxide; sodium picrate is the product. It should be carefully noted that the nitration of phenol makes it a *stronger acid;* the nitration of aniline makes it a *weaker base*.

Negative Groups. A list of those groups which make ammonia less basic is useful in making approximate predictions as to the basic strength of organic amines. These groups are sometimes called *negative groups* and they are arranged below in what might be called an order of *increasing negativity*, the last group being the most effective.

$$C_6H_5-;\ p\text{-}NO_2C_6H_4-;\ \underbrace{CH_3CO-;\ 2,4(NO_2)_2C_6H_3-;\ (NO_2)_3C_6H_2-}_{\text{Increasing negativity}}$$

The other acyl groups such as propionyl and butyryl would be placed with the acetyl group. All these groups are unsaturated groups, and the unsaturation is at the point of attachment of the group. It must be borne in mind that all these groups exert their influence only if *directly* linked to the nitrogen atom. The *indirect influence* of the nitro group in aromatic compounds, which is transmitted through the ring, should not be confused with the direct effect of negative groups.

The following table gives the basic dissociation constants of the $-NH_2$ compounds which correspond to the negative groups listed above. The right-hand side of the table lists the corresponding OH compounds and their acid dissociation constants. It will be recalled that water is a very weak acid ($K_A = 1 \times 10^{-14}$) and ammonia a moderately strong base ($K_B = 2 \times 10^{-5}$). Introducing the weakly negative phenyl group in place of one hydrogen atom of water makes a very weak acid, while introduc-

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Group	*Ammonia Derivative*	K_B	*Water Derivative*	K_A
C_6H_5-	$C_6H_5NH_2$	3.5×10^{-10}	C_6H_5OH	1.7×10^{-10}
p-$NO_2C_6H_4-$	p-$NO_2C_6H_4NH_2$	1.0×10^{-12}	p-$NO_2C_6H_4OH$	6.4×10^{-8}
CH_3CO-	CH_3CONH_2	*	CH_3COOH	1.8×10^{-5}
$2,4(NO_2)_2C_6H_3-$	$(NO_2)_2C_6H_3NH_2$	*	$(NO_2)_2C_6H_3OH$	1.0×10^{-4}
$(NO_2)_3C_6H_2-$	$(NO_2)_3C_6H_2NH_2$	*	$(NO_2)_3C_6H_2OH$	1.6×10^{-1}

* Too weak to form salts in water solutions. The K_B of CH_3CONH_2 has been estimated as 1×10^{-15}; that of $(NO_2)_2C_6H_3NH_2$ as less than 10^{-16}.

ing the strong negative group $(NO_2)_3C_6H_2-$ produces a strong acid. The effect on the basicity of ammonia is just the reverse; the more negative the group the less basic is the $-NH_2$ compound. A careful study of the table will show that the two effects of the negative groups are approximately the same numerically; thus, para nitroaniline is about 100 times (10^2) as weak a base as aniline and para nitrophenol is about 100 times as strong an acid as phenol.

Benzyl Amine. The aryl amines are usually considered to include only those compounds in which one or more aryl groups are *directly* attached to the nitrogen atom. For this reason, benzylamine, $C_6H_5CH_2NH_2$, is not classified as an aryl amine although it contains an aryl group. In fact, it has nothing in common with the aryl amines; its method of preparation and all its reactions are evidence of its close relationship to the aliphatic amines. For example, it may be prepared by the action of ammonia on benzyl chloride. On treating with nitrous acid it behaves like a typical aliphatic primary amine (p. 189) and not like aniline; it does not form a diazonium salt but evolves nitrogen. Its basic strength ($K_B = 2 \times 10^{-5}$) is not strikingly different from that of an aliphatic primary amine (CH_3NH_2, $K_B = 50 \times 10^{-5}$), which, it will be recalled, is much greater than that of the aryl amines (about 10^{-10}). A comparison of benzylamine and the isomeric toluidines ($CH_3C_6H_4NH_2$) is instructive, and, like the contrast between chlorotoluene and benzyl chloride (p. 521), illustrates that the characteristic peculiarities of aryl compounds are confined to those substances in which the functional group (or atom) is directly attached to the aromatic nucleus.

INTERMEDIATE REDUCTION PRODUCTS OF NITROBENZENE

The final reduction product of an aromatic nitro compound is a primary amine. Thus, as we have seen, the reduction of nitrobenzene

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with metals and acid yields aniline. By using less drastic reducing agents it is possible to isolate two substances intermediate between nitrobenzene and aniline; these are nitrosobenzene, C_6H_5NO, and phenylhydroxylamine, C_6H_5NHOH. (The name of the latter substance follows from its relation to hydroxylamine, NH_2OH.) If the reduction of nitrobenzene is carried out in an alkaline solution, these two compounds condense and the final products are either azoxybenzene, $C_6H_5N = \overset{\overset{O}{\uparrow}}{N}C_6H_5$, azobenzene, $C_6H_5N = NC_6H_5$, or hydrazobenzene, $C_6H_5NHNHC_6H_5$. As there is some interesting chemistry connected with each one of these substances, they warrant a brief consideration.

Nitrosobenzene and Phenylhydroxylamine. By the action of zinc dust and water on nitrobenzene, one oxygen atom is removed and nitrosobenzene results. This latter compound

$$C_6H_5NO_2 + Zn \longrightarrow C_6H_5NO + ZnO$$

very readily combines with two hydrogen atoms so that, unless special precautions are taken, phenylhydroxylamine, C_6H_5NHOH, is the final product.

$$C_6H_5N = O + 2[H] \xrightarrow[H_2O]{Zn} C_6H_5NHOH$$

Phenylhydroxylamine can be oxidized to nitrosobenzene by the action of aqueous chromic acid, and this is perhaps the best method of preparing the nitroso compound.

$$C_6H_5NHOH + [O] \xrightarrow{H_2CrO_4} C_6H_5N = O + H_2O$$

Phenylhydroxylamine undergoes a molecular rearrangement when treated with acids to give para aminophenol (p. 474).

Nitrosobenzene is a colorless, crystalline solid which melts at 68° to a blue-green liquid. Solutions of nitrosobenzene are also colored. It has been shown that this and other nitroso compounds exist in a colorless, dimolecular form (two molecules associated together) as well as in the colored simple molecule. The crystalline nitrosobenzene is probably entirely the dimolecular form.

The nitroso group is very reactive, and nitroso compounds undergo condensation reactions with many substances containing an "active hydrogen" attached to a carbon atom. Since para nitrosodimethylaniline (p. 445) is more readily prepared than nitrosobenzene, and is more stable, its condensation reactions are of more im-

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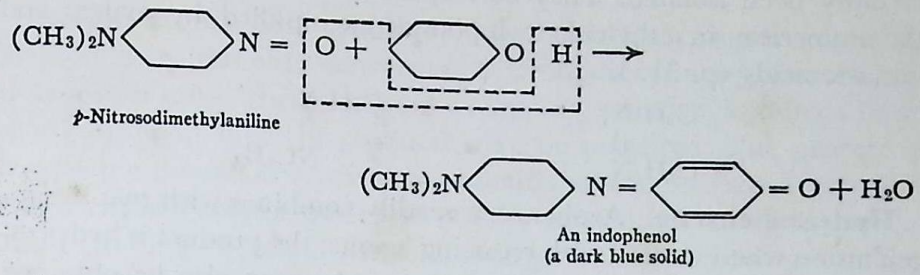
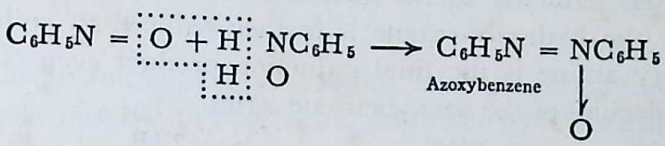
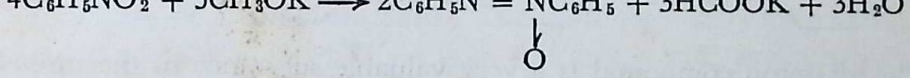
portance than those of the parent substance. As an illustration, the condensation with phenol may be written.



Azoxybenzene and Azobenzene. The condensation of one molecule of nitrosobenzene and one molecule of phenylhydroxylamine produces azoxybenzene. As the isolation of the two reactants in the



above equation is somewhat difficult, it is more convenient to prepare azoxybenzene directly from nitrobenzene in one operation. By heating the nitro compound with potassium methoxide, the reduction proceeds only as far as the nitroso and phenylhydroxylamine stage; these then condense rapidly in the alkaline medium, forming azoxybenzene. Azoxybenzene is a bright yellow solid melting at 36°.



The oxygen atom of azoxybenzene is easily removed by heating the compound with iron filings; **azobenzene,** $C_6H_5N = NC_6H_5$, results. The more convenient and usual method of preparation of azobenzene is to reduce nitrobenzene with an alkaline solution of stannous chloride (sodium stannite). This reducing agent probably first forms azoxybenzene by the mechanism given above, and then reduces this substance to azobenzene. Azobenzene is a bright red solid (mp 67°). It is the parent substance of a large class of compounds, some of which are important dyes (p. 460). Compounds which contain the grouping $-N = N-$ between two benzene nuclei are named as derivatives of azobenzene; almost none of them are prepared from the parent compound azobenzene, however, which is therefore of little practical importance. It is, however, of considerable scientific interest for, as the construction of models will show, azo-

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benzene should exist in the two forms shown below. Both forms have recently been isolated. They correspond for the N = N linkage to the isomerism in ethylenic compounds exemplified by maleic and fumaric acids (p. 315).

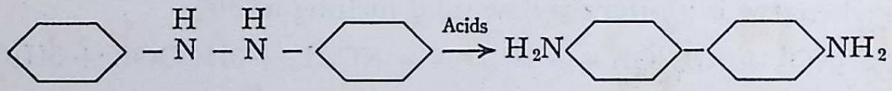
$$\begin{array}{c} C_6H_5N \\ \| \\ C_6H_5N \end{array} \qquad\qquad \begin{array}{c} C_6H_5N \\ \| \\ NC_6H_5 \end{array}$$

Hydrazobenzene. Azobenzene readily combines with two hydrogen atoms when treated with reducing agents; the product is hydrazobenzene, $C_6H_5NHNHC_6H_5$. Hydrazobenzene can also be obtained directly from nitrobenzene by reduction with zinc and sodium hydroxide.

If vigorous reducing agents such as a metal-acid combination are employed, the hydrazobenzene is further reduced to aniline. Thus the primary amine is the final reduction product even of the condensed molecules of the azoxybenzene series.

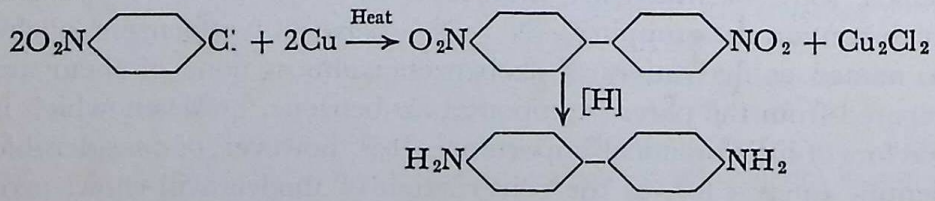
$$C_6H_5N{=}NC_6H_5 \xrightarrow[\text{Zn and NaOH}]{2[H]} C_6H_5NHNHC_6H_5 \xrightarrow[\text{Zn and acid}]{2[H]} 2C_6H_5NH_2$$

Benzidine. When hydrazobenzene is treated with mineral acids, it undergoes a rearrangement to form benzidine, a colorless solid melting at 128°.



This diamino compound is a very valuable substance in the preparation of certain dyes. It is prepared in quantity by reducing nitrobenzene to hydrazobenzene by the action of zinc dust and aqueous sodium hydroxide. The hydrazobenzene when treated with acid rearranges to benzidine.

Structure of Benzidine. The method of preparation of benzidine obviously tells us nothing about its structure. The synthesis of benzidine from para chloronitrobenzene proves that it is 4,4′-diaminobiphenyl. This synthesis is not an industrial process; the steps are as follows:



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THE DIAZONIUM SALTS

Diazotization. The synthesis of aromatic compounds is greatly facilitated by the easy conversion of aromatic primary amines into **diazonium salts.** These compounds are very reactive, and from them many different types of products may be prepared. The process of converting the salt of a **primary aromatic amine** into the **diazonium salt** is called **diazotization.** It is usually carried out by dissolving the amine in dilute aqueous acid and adding a solution of sodium nitrite. It is necessary to keep the temperature low, as otherwise both the nitrous acid and the diazonium salt may decompose.

$$C_6H_5NH_3Cl + HNO_2 \longrightarrow C_6H_5\underset{\underset{N}{|||}}{N}Cl + 2H_2O$$

The aqueous solutions of diazonium salts are usually so unstable that it is not possible to obtain the solid salt by evaporation. Such crystalline salts, however, may be prepared by diazotization in glacial acetic acid and precipitation with ether, in which they are insoluble. For this purpose an organic ester of nitrous acid, such as **butyl nitrite,** is used instead of sodium nitrite.

$$C_6H_5NH_3Cl + C_4H_9ONO + CH_3COOH \longrightarrow C_6H_5N_2Cl + C_4H_9OCOCH_3 + 2H_2O$$

The dry diazonium salts are easily detonated.

Structure of Diazonium Salts. The diazonium salts may be represented as ArN_2X, in which Ar is an aryl group, such as phenyl, and X, an acid group. In solution, they are dissociated into the ions $ArN_2^+ + X^-$. The formula $C_6H_5 - \underset{\underset{N}{|||}}{N} - Cl$ is usually preferred to $C_6H_5N = N - Cl$. The substance, $C_6H_5N_2Cl$, is called *benzenediazonium chloride*. The reactions of a diazonium salt are thus essentially the reactions of the diazonium ion. This ion is very unstable and reactive and undergoes varied transformations which depend on the conditions.

The problem of the structure of the diazonium salts is the problem of the position of the positive charge on the diazonium ion. In other words, the location of an electron is involved. The two formulas

$$C_6H_5 : \underset{\underset{N:}{\vdots\vdots}}{N^+} \quad \text{and} \quad C_6H_5 : \underset{\underset{N^+}{\vdots\vdots}}{N} :$$

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represent two resonating structures and the ion is a resonance hybrid.

Reactions of Diazonium Salts. The following reactions of diazonium salts are of great synthetic value. Although they will be illustrated by considering benzenediazonium chloride, it is important to bear in mind that *a diazonium salt from any primary aromatic amine* will behave in the same manner.

1. The Replacement of N_2X by OH.

This is brought about by heating an aqueous solution of the diazotized amine. The solution should be strongly acid to avoid the coupling reaction between phenol and undecomposed diazonium salt, a reaction which is discussed on page 457.

$$C_6H_5N_2Cl + H_2O \longrightarrow C_6H_5OH + N_2 + HCl$$

2. The Replacement of N_2X by H.

Some diazonium salts are converted to the corresponding hydrocarbon by heating them with ethyl alcohol.

$$C_6H_5N_2Cl + C_2H_5OH \xrightarrow{\text{Heat}} C_6H_6 + N_2 + HCl + CH_3CHO$$

This method is not general since very frequently an ether is formed.

$$C_6H_5N_2Cl + C_2H_5OH \longrightarrow C_6H_5OC_2H_5 + N_2 + HCl$$

With benzenediazonium chloride a mixture of the hydrocarbon and ether is formed. The course of the reaction of diazonium salts with alcohols depends largely on the nature of the alcohol, the diazonium salt, and on the conditions of experiment.

A more general procedure for the conversion of a diazonium salt to the corresponding hydrocarbon is treatment with hypophosphorous acid.

$$C_6H_5N_2Cl + H_3PO_2 + H_2O \longrightarrow C_6H_6 + H_3PO_3 + HCl + N_2$$

3. The Replacement of N_2X by Halogens.

In this reaction the solution is kept as concentrated as possible and 1 mole of cuprous salt and a considerable amount of halogen acid are added. A complex compound between the cuprous salt and the diazonium salt is first formed and often precipitates. This slowly decomposes and yields the aryl halide and nitrogen.

$$C_6H_5N_2Cl + Cu_2X_2 + HX \longrightarrow C_6H_5X + N_2 + HCl + Cu_2X_2$$

Where X = Cl or Br

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The introduction of an iodine atom does not require the use of a cuprous salt. Hydrogen iodide or its salts may be used.

4. Replacement of N_2X by CN.

This reaction takes place when sodium cyanide and cuprous cyanide are used.

$$C_6H_5N_2Cl + Cu_2(CN)_2 + NaCN \longrightarrow C_6H_5CN + N_2 + NaCl + Cu_2(CN)_2$$

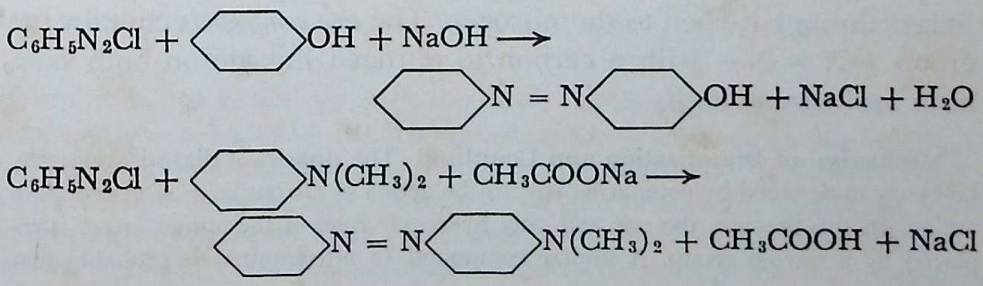
The preceding two reactions are often called the *Sandmeyer reaction.* If finely divided copper is used as the catalyst, the reaction is known as the *Gattermann reaction.*

Phenylhydrazine, $C_6H_5NHNH_2$. When an aqueous solution of benzenediazonium chloride is reduced, the hydrochloride of phenylhydrazine is formed.

$$C_6H_5N_2Cl + 4[H] \longrightarrow C_6H_5NHNH_3Cl$$

Stannous chloride in hydrochloric acid or sodium sulfite are the usual reducing agents employed. The free base can be prepared from the salt in the usual manner. Phenylhydrazine may be considered as the phenyl derivative of the inorganic base **hydrazine,** NH_2NH_2. It has been of great value in the laboratory because it reacts with ketones and aldehydes forming crystalline compounds called *phenylhydrazones.* These have proved very useful in the identification and isolation of ketones and aldehydes (p. 143). Indeed, the discovery of phenylhydrazine by Emil Fischer in 1875 enabled him to make great advances in our knowledge of the carbohydrates (p. 285).

The Coupling of Diazonium Salts. The usefulness of the diazonium salts is not exhausted with the replacement reactions we have just considered. This remarkable class of compounds is also the basis of one branch of the synthetic coal-tar dye industry. The azo dyes are all prepared by the so-called coupling of diazonium salts. This coupling reaction takes place when a *phenol* or *aryl amine* is treated with a diazonium salt solution. Sodium acetate, sodium carbonate, or sodium hydroxide is added to make the mixture less acid.



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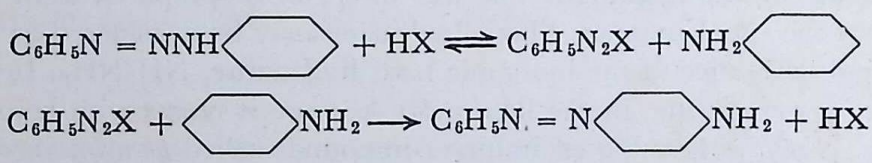
It will be noted, in the examples given above, that the coupling reaction has taken place in the para position. The ortho and para hydrogen atoms in phenols and tertiary amines are reactive and, therefore, the process takes place with these compounds. Hydrocarbons, with only a few exceptions, will not couple with diazonium salts. If a primary or secondary aryl amine is used, the coupling takes place on the nitrogen atom.

$$C_6H_5N_2Cl + C_6H_5NH_2 + CH_3COONa \longrightarrow C_6H_5N = NNHC_6H_5 + NaCl + CH_3COOH$$

On heating the resulting compound in weakly acid solution or with aniline hydrochloride, a rearrangement occurs, and a product is formed, $C_6H_5N = NC_6H_4NH_2$, which corresponds to that produced by direct para coupling with the tertiary amine.

The mechanism of this process involves the hydrolysis of the diazoamino compound back to the diazonium salt and amine which then slowly couple the other way round.



Ordinarily, the coupling of primary and secondary amines is carried out in slightly acid medium. Under these conditions direct para or ortho coupling occurs.

Nomenclature of Azo Compounds. The substances produced by coupling a diazotized aryl amine and a phenol or tertiary amine are derivatives of azobenzene. Thus, the product of the interaction of diazotized aniline and phenol is called *p-hydroxyazobenzene;* the compound from dimethylaniline and benzenediazonium chloride is *p-dimethylaminoazobenzene.* The compound first formed in the coupling of aniline and diazotized aniline, $C_6H_5N_2NHC_6H_5$, is known as *diazoaminobenzene.* In general, *diazo compounds* contain the grouping $ArN = N - Z$, where Ar is any aryl group and Z any group not linked through carbon to the nitrogen. The *azo compounds* contain the group $-N = N-$ with a carbon to nitrogen linkage on both sides as in azobenzene itself.

Mechanism of Diazotization and Coupling. The process of diazotization may be better understood by comparing it with the action of nitrous acid on a secondary amine. In this reaction the one and only hydrogen atom of the amino group is replaced by a nitroso group. A similar compound (a nitrosamine) is probably first

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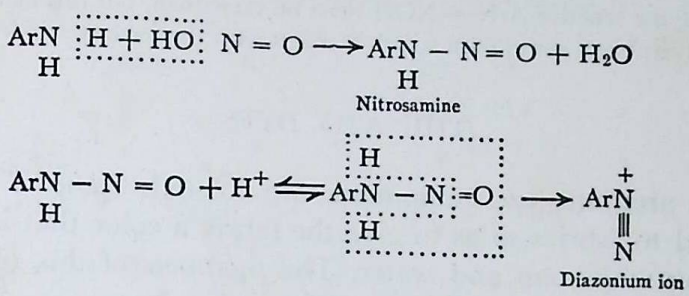
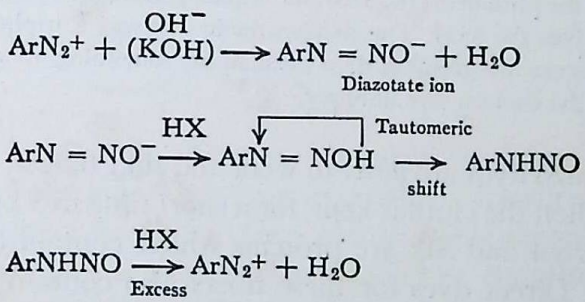
formed in the diazotization of a primary amine, but an excess of mineral acid converts it at once into the diazonium salt. The reactions may be formulated in the following way.

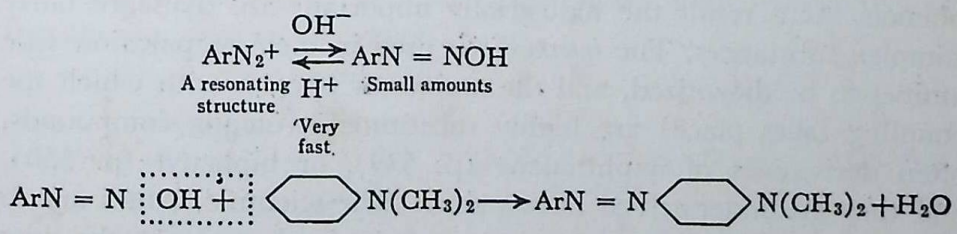


It is very difficult to prove that the reaction takes the course pictured above, but the nitrosamines, ArNHNO, can be prepared by the action of dilute alkali on the diazonium salts, followed by cautious acidification. Excess of mineral acid indeed does convert the nitrosamine into the diazonium salt so that a complete cycle may be carried out.



The diazotates are the salts of the unstable acid ArN = NOH; the salts are stable substances and are usually known in two forms whose existence has been explained on the basis of geometrical isomerism.

The coupling reactions of the diazonium salts proceed through the formation of the compound ArN = NOH. Written as an ionic reaction, the equations are:



These equations enable one to picture more readily the formation of an azo compound from a diazonium salt. The diazonium ion predominates in the equilibrium in even neutral solutions because of its relative stability due to the resonance energy. The function of the sodium acetate which must be added to bring about the coupling with amines or the alkali which must be present in the case of the phenols is readily explained. These inorganic reagents regulate the hydroxyl ion concentration

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of the aqueous solution, and thus provide a continually sufficient concentration of the reactive $C_6H_5N = NOH$. The less acid the solution the more rapid the coupling; at the acidity of acetic acid (obtained by adding an excess of sodium acetate), the concentration of the reactive $ArN = NOH$ must be very small, but this fact is counterbalanced by the great speed with which it reacts with the tertiary amine.

THE AZO DYES

All the aromatic azo compounds are colored. Some of them can be applied to fabrics so as to give the fabric a color that is resistant to washing with soap and water. The members of this second and smaller group are dyes: more specifically, azo dyes.

The azo dyes constitute just one of several large classes of synthetic dyes. Almost all these dyes are aromatic compounds and, consequently, they are referred to collectively as *coal-tar dyes*. We shall have occasion later to mention certain other groups of organic dyes: the phthaleins (p. 510), the triphenylmethane dyes (p. 531), and the anthraquinone dyes (p. 555). The first synthetic dye was a triphenylmethane dye and when we discuss this group of dyes we shall say something about the origin and development of the coal-tar dye industry.

The useful azo dyes are *direct* to wool and silk; that is, they will dye these fibers when the cloth is kept for a short time in a boiling solution of the dye. Wool and silk are proteins which contain both acid and basic groups. Direct dyes for these fibers also contain acid or basic groups. Acid azo dyes usually contain the sulfonic acid group, which also makes the dye soluble in water; basic azo dyes usually contain the dialkylamino group.

The azo dyes are prepared by the coupling reaction described above, but starting with more complex diazonium salts, amines, and phenols. As a result the industrially important azo dyes are fairly complex substances. The *intermediates* used in their preparation (the amines to be diazotized, and the amines or phenols with which the coupling takes place) are highly substituted aromatic compounds, often derivatives of naphthalene (p. 539), or biphenyl (p. 550), and they go under trivial names since their scientific names are so cumbersome. This is even more true of the final products, the dyes themselves.

A typical acid dye is Orange II (note the name!), prepared by coupling diazotized sulfanilic acid with β-naphthol (a hydroxyl derivative of naphthalene quite analogous to phenol).

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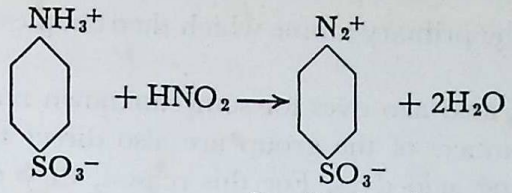
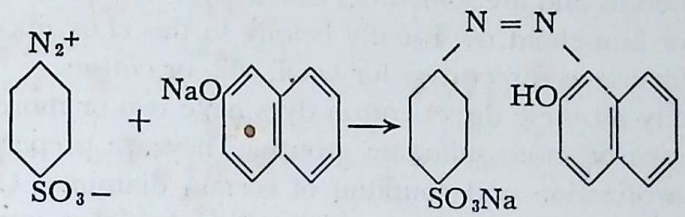
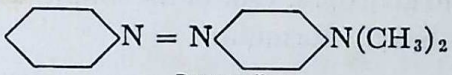


Inner diazonium salt



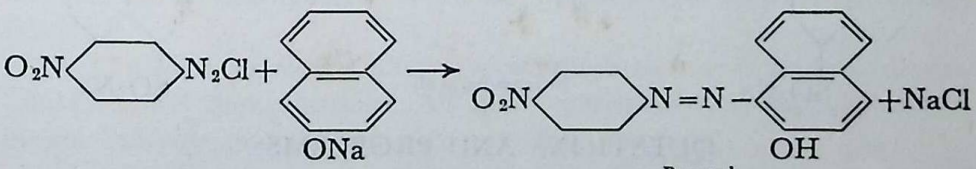
Orange II

A typical basic azo dye is *butter yellow*, prepared by coupling benzene diazonium chloride with dimethylaniline. Its scientific name is *p*-dimethylaminoazobenzene.



Butter yellow

Azo Dyes for Cotton. Cotton, essentially cellulose, is a neutral substance, and the acid and basic dyes which are direct to silk and wool are not direct to cotton. They can be made direct to cotton by a special method of application in which the coupling reaction to form the dye is carried out in the fibers of the cloth. This may be done by impregnating the cloth with an alkaline solution of a phenol or amine and then passing the cloth through a solution of the diazonium salt. Dyes produced in this way are known as *ingrain colors.* If cloth is impregnated with an alkaline solution of β-naphthol and then passed through a solution of diazotized para nitroaniline the ingrain dye, *para red*, is formed.



Para red

A variant of this procedure leads to the **developed dyes.** A cloth is dyed with a dye which contains a primary amino group. The cloth is then led through a cold dilute solution of nitrous acid, and then at once through an alkaline solution of a phenol or an amine. The nitrous

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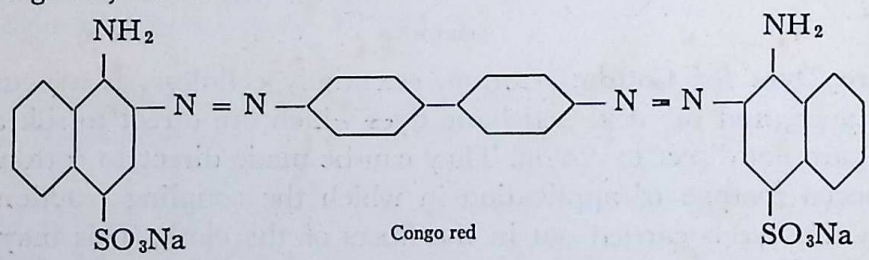
acid diazotizes the primary amine which then couples with the phenol or amine.

One group of acid azo dyes for some unknown reason is direct to cotton. The members of the group are also direct to wool and silk by virtue of being acid dyes. For this reason, they may be used on mixed materials and are sometimes called *union colors*. The dyes which are sold for household use usually belong to this class since they are designed for use as direct dyes for wool, silk, or cotton.

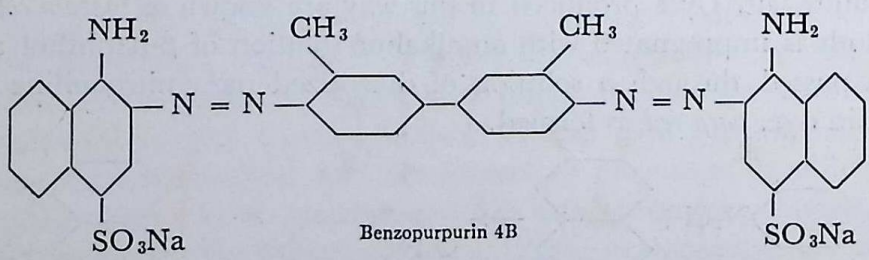
Practically all these direct cotton dyes have two or more azo linkages and two or more sulfonate groups. They are prepared by the double diazotization and coupling of certain diamines. One of the most important of the diamines which will form direct cotton dyes is **benzidine** (p. 454).

The two primary amino groups in this compound can be diazotized in the usual way, and the di-diazonium salt coupled with sulfonated phenols or amines to give dyes. One of the simplest of these compounds is *Congo red*, which has the formula:



Congo red

The closely related Benzopurpurin 4B is one of the most important direct cotton colors.



Benzopurpurin 4B

QUESTIONS AND PROBLEMS

1. What is the inner salt formula for sulfanilic acid? Why is this formula written for the compound? What other substances which exist as inner salts have you encountered earlier in this course?

2. Write structural formulas for 2-hydroxy-4-nitrotoluene, ethyl-diphenyl-amine, benzidine, *p*-nitroazobenzene, 2,4,6-trinitroaniline, 3,5-dinitrochlorobenzene, tri-*p*-tolylamine, diazoaminobenzene.

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3. Write a structural formula for a nitroamine and for a nitramine.

4. Outline the steps in the synthesis of the following compounds from coal-tar crudes: (*a*) meta nitroaniline, (*b*) benzidine, (*c*) meta nitrophenol, (*d*) phenylhydroxylamine, (*e*) acetanilide.

5. Write balanced equations for the action of nitrous acid on $C_6H_5NHCH_3$, $CH_3CH_2CONH_2$, CH_3NH_2, $C_6H_5N(C_2H_5)_2$, $CH_3NHC_2H_5$, $CH_3NHCOOC_2H_5$, *p*-$BrC_6H_4NH_2$, and $(CH_3)_2NC_2H_5$.

6. Write structural and electronic formulas for benzenediazonium chloride. How are diazonium salts prepared?

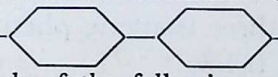
7. Outline the steps in the synthesis from coal-tar crudes of two aromatic nitro compounds which are of importance as high explosives.

8. Write equations for the replacement reactions of *p*-nitrobenzenediazonium chloride.

9. Why is *p*-hydroxyazobenzene not a dye, though it is a deeply colored compound?

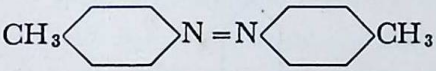
10. Outline the intermediate steps in the reduction of nitrobenzene.

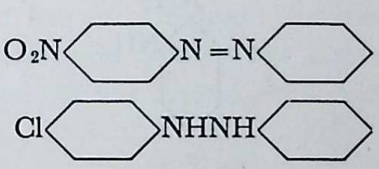
11. Compare and contrast the following pairs of compounds: (*a*) 2,4-dinitrophenol and phenol, (*b*) 3,5-dinitrochlorobenzene and chlorobenzene, (*c*) 2,4,5-trinitroaniline and aniline.

12. What reactions of benzidine would you use to prove that it has the structure 

?

13. Name each of the following compounds and indicate a method of synthesizing it.





14. What types of azo dyes are fast to wool and silk? Can you offer an explanation for the fact that these dyes are fast to wool and silk, but not to cotton?

15. What group of azo dyes are fast to cotton? How can other groups of azo dyes not ordinarily fast to cotton be applied so that they are fast to that fabric?

16. Outline a chemical method of separating a mixture of picric acid, para toluidine, and dinitrobenzene. All three compounds are solids, soluble in organic solvents, and only sparingly soluble in water.

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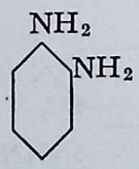
Chapter 24

DIAMINES, POLYHYDROXY COMPOUNDS, AND AMINOPHENOLS

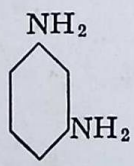
These compounds find wide use as dye and drug intermediates and as photographic developers. They are similar in some of their reactions. For these reasons they are considered together in this chapter.

THE DIAMINES

The diamino derivatives of benzene are known as the *phenylene diamines*. The nomenclature is peculiar and is based on the concept of $C_6H_4\langle$ as a "phenylene group" analogous to $CH_2\langle$, the methylene group of the aliphatic series. The three isomeric phenylene diamines have the physical properties noted below:



Ortho phenylene diamine
bp 252°
mp 102°



Meta phenylene diamine
bp 287°
mp 62°

Para phenylene diamine
bp 267°
mp 140°

All three substances are slightly soluble in cold water but soluble in warm water and a variety of organic solvents. They are easily oxidized, becoming darkly colored on standing in the air. They are weak bases of about the strength of aniline and will combine with one or two molecules of an acid to form salts. They react with nitrous acid to form diazonium salts, which then undergo condensation to complex compounds. For this reason the diamines are not used in the synthesis of other disubstituted benzenes.

Industrial Preparation and Uses. The meta phenylene diamine is prepared by the complete reduction of meta dinitrobenzene, which, in turn, is prepared from benzene.

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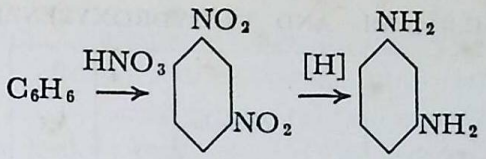
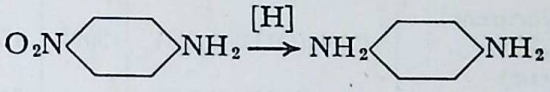
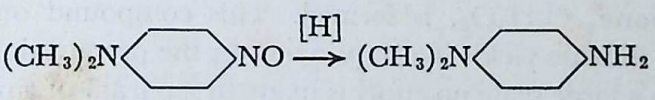


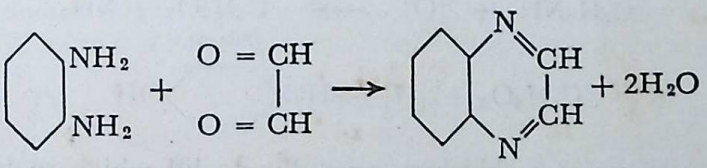
The ortho and para phenylene diamines are prepared from the corresponding nitroanilines by reduction. (The *o*- and *p*-nitroanilines may be prepared by the method on page 448, or by treating ortho and para nitrochlorobenzenes with ammonia.)



The diamines couple with diazonium salts to furnish azo dyes; they are among the important dye intermediates. Not only the diamines themselves, but also the dimethyl derivatives are used. The latter are prepared by the reduction of the corresponding nitro or nitroso dimethylanilines. The para nitrosodimethylaniline is readily prepared from dimethylaniline (p. 445).



Ortho phenylene diamine finds special use as a reagent for the identification of α or 1,2-dicarbonyl compounds. With these compounds it forms quinoxaline derivatives, which are crystalline solids having sharp melting points.



Quinoxaline

POLYHYDROXY COMPOUNDS

General Characteristics. The derivatives of benzene with two or more hydroxyl groups attached to the ring resemble phenol in their chemical behavior. They are very weak acids and give a characteristic color with ferric chloride. As would be expected from the number of hydroxyl groups, they are readily soluble in water. The isomeric di- and trihydroxybenzenes are listed on page 466 together with their physical properties.

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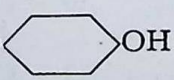
ISOMERIC DI- AND TRIHYDROXYBENZENES

Name	*Formula*	*Boiling Point*	*Melting Point*	*Solubility Grams per 100 Grams of Water at 20°*
Pyrocatechol (*o*-Dihydroxybenzene)	$C_6H_4(OH)_2(1,2)$	245°	105°	24
Resorcinol (Resorcin) (*m*-Dihydroxybenzene)	$C_6H_4(OH)_2(1,3)$	277°	110°	147
Hydroquinone (*p*-Dihydroxybenzene)	$C_6H_4(OH)_2(1,4)$	286°	171°	6.5
Pyrogallol (1,2,3-Trihydroxybenzene)	$C_6H_3(OH)_3(1,2,3)$	309°	134°	60
Phloroglucinol (1,3,5-Trihydroxybenzene)	$C_6H_3(OH)_3(1,3,5)$		219°	Very soluble
1,2,4-Trihydroxybenzene	$C_6H_3(OH)_3(1,2,4)$		141°	

Preparation of Hydroquinone. Hydroquinone, $C_6H_4(OH)_2$ (1,4) is prepared from aniline. When aniline is oxidized with potassium dichromate and sulfuric acid, a yellow, volatile solid, **quinone** or **benzoquinone,** $C_6H_4O_2$, is formed. This compound on reduction with sulfur dioxide yields hydroquinone. In the preparation of hydroquinone on a large scale no effort is made to separate the intermediate compound; it is at once distilled with steam from the reaction mixture and reduced with iron and acid. The hydroquinone is obtained as a crystalline mass on concentrating the solution.

$$C_6H_5NH_2 + 2[O] \xrightarrow{K_2Cr_2O_7} \underset{\text{Quinone}}{C_6H_4O_2} + NH_3$$

$$C_6H_4O_2 + 2[H] \longrightarrow$$ 

Hydroquinone is a colorless, crystalline solid which melts at 171° to a liquid which boils at 286°. It may be purified by crystallization or distillation under diminished pressure. It finds wide use as a photographic developer.

Quinone (1,4-Benzoquinone). If we examine the intermediate substance, quinone, we find that it is a yellow, crystalline solid (mp 116°) with a penetrating odor. It does not behave like an aromatic compound. On the contrary, it shows the typical reactions of an olefin hydrocarbon and an aliphatic ketone. For example, it combines with four atoms of bromine to form a tetrabromide, and reacts with hy-

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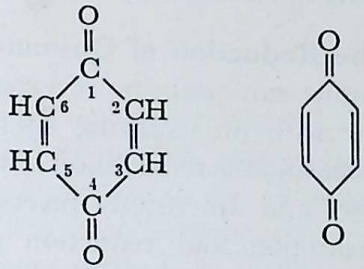
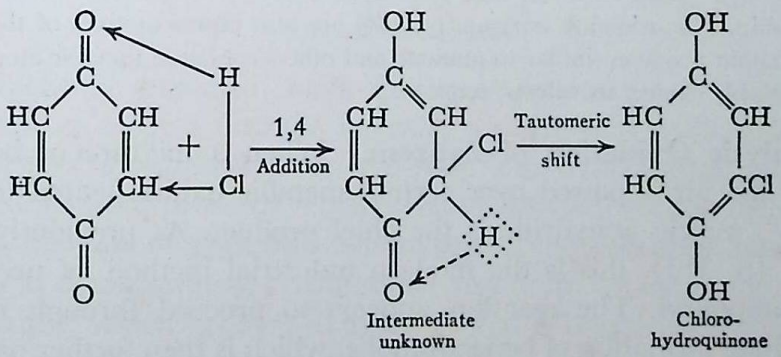
droxylamine forming a dioxime. Taking into account these facts and its easy conversion into para dihydroxybenzene (whose structure is definitely established by other syntheses), we can write the following formula with considerable confidence. (The outline formula on the right is frequently employed.)



It will be noted that in this compound the double linkages are indicated as being definitely in the 2,3 and 5,6 positions, and that, unlike benzene, and its derivatives, two of the six carbon atoms are attached to a divalent atom (oxygen). Although quinone is formed by the oxidation of an aromatic compound and passes into a member of this class on reduction, it is itself *not a typical aromatic substance.* **Quinone is an unsaturated, cyclic ketone,** an alicyclic compound.

Quinone contains a conjugated system of double linkages. Unlike benzene, however, the conjugated system is not complete and symmetrical, but has two oxygen atoms at the ends. In many of its reactions quinone is very similar to the α,β-unsaturated ketones discussed in Chap. 16. Carbonyl reagents react both normally with the carbonyl group (1,2-addition) and also abnormally, yielding 1,4-addition products, as they do with the α,β-unsaturated ketones (p. 320). The reaction of hydrogen chloride and quinone is of the latter type; a chlorohydroquinone is the product.



Quinhydrone. When hydroquinone and quinone are present in solution they form the very dark brown molecular compound, quinhydrone, $C_6H_4O_2 \cdot C_6H_4(OH)_2$. This may be obtained in greenish black crystals by evaporation of the solution. The

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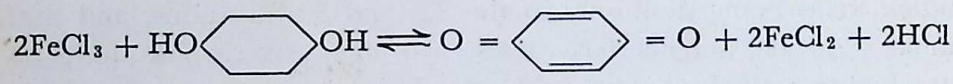
compound is usually prepared by the partial oxidation of hydroquinone. In solution it is largely dissociated into its components, quinone and hydroquinone. The speed of the dissociation is so rapid that no characteristic reactions of quinhydrone are known; it behaves chemically like a mixture of quinone and hydroquinone. The exact nature of the valence forces which hold the two molecules together in quinhydrone is unknown. Other so-called molecular compounds are known; for example, the addition compounds of picric acid and the aromatic hydrocarbons (p. 440).

Reversibility of the Reduction of Quinone. The change from quinone to hydroquinone can easily be reversed in acid solution by treating hydroquinone with an oxidizing agent. The reduction of quinone to hydroquinone and the reoxidation of the latter are extraordinarily rapid processes and are strictly reversible. This is one of the relatively few oxidation and reduction reactions of organic chemistry which is rapid and reversible like the oxidation and reduction of inorganic ions.



If a platinum wire is dipped into a solution of quinone and hydroquinone in a conducting solvent (e.g., dilute acid), a definite electrical potential is developed on the wire. Such a system will serve as one half of an electric battery provided a conducting liquid connects it with another "half cell" (e.g., a piece of zinc dipping in dilute acid). The potential of the inert electrode (platinum wire) is found to depend in a precise way on the relative amounts of quinone and hydroquinone in the solution. Other quinones (see below) and their corresponding hydroquinones, certain dyes and their reduction products, and a few other classes of organic compounds show this same behavior. Mixtures of reduced and oxidized inorganic ions (e.g., ferrous and ferric) usually develop a potential in the same way, but most combinations of organic systems do not. The quinone-hydroquinone system is a representative of a special class in which there is an easily reversible oxidation-reduction relationship. The oxidizing enzymes (p. 384) are also representatives of this class; some contain a system similar to quinone and others contain a metallic atom which can reversibly change its valence state.

Catalytic Oxidation of Benzene. When a mixture of benzene vapor and air is passed over certain metallic oxides heated to 400° to 500°, maleic anhydride is the chief product. As previously mentioned (p. 313), this is the modern industrial method of preparing this compound. The reaction appears to proceed through the intermediate formation of benzoquinone, which is then further oxidized to maleic acid. Indeed, under certain conditions, benzoquinone can be isolated from the product. It has been known for a long time that with certain oxidizing agents benzoquinone is oxidized to maleic acid.

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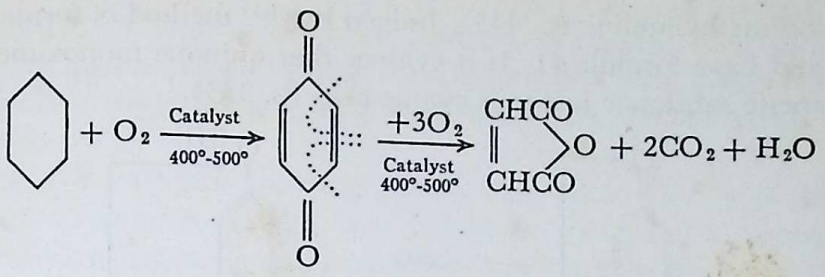
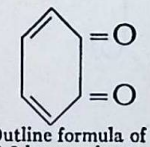
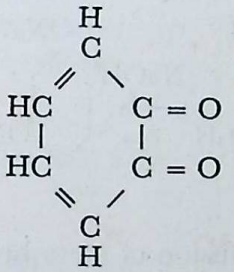


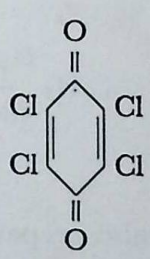
Other Quinones. The substance referred to above as quinone is more correctly called 1,4- or *para benzoquinone*. The nomenclature shows that the oxygen atoms are in the 1,4 or para position and that the compound is derived from benzene. One other benzoquinone is known; this is the 1,2- or **ortho benzoquinone,** which is formed by oxidizing the corresponding dihydroxy compound. A great variety of substituted 1,4- and 1,2-benzoquinones are known, as well as quinones related to other polycyclic aromatic hydrocarbons (p. 552). **Chloranil** or tetrachloro-para-benzoquinone (mp 290°) is a yellow solid formed by treating a great variety of organic compounds, such as aniline or phenol, with potassium chlorate and hydrochloric acid (a chlorinating and oxidizing mixture). It finds use as a fungicide.



Outline formula of 1,2-benzoquinone



Ortho or 1,2-benzoquinone



Chloranil

As might be expected, meta quinones are unknown, since it is impossible to write a formula for such a compound without having free linkages or a bridge across the ring. The oxidation of meta hydroxy compounds proceeds readily, but yields complex products.

Tautomerism of Quinone Monoxime. The diketonic nature of quinone is demonstrated, among other reactions, by the formation of the dioxime, which behaves in every way as a ketonic oxime should. It is also possible to obtain a monoxime from quinone by the action of hydroxylamine. This substance would be expected to have the formula I, below. It is identical, however, with the product obtained by the action of nitrous acid on phenol or by the decomposition of

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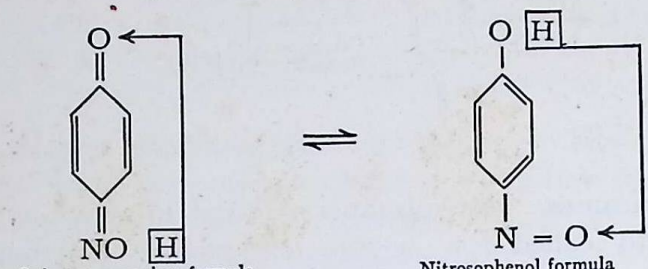
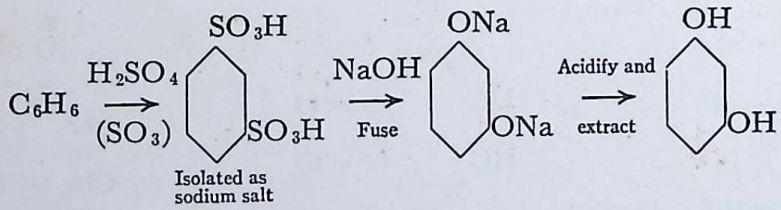
nitrosodimethylaniline (p. 445). Judged by this method of formation, it should have formula II. It is evident that quinone monoxime is a tautomeric substance just as is cyanic acid (p. 333).



Quinone monoxime formula I — Nitrosophenol formula II

Whether the one substance which is known is to be represented by formula I or II is still uncertain; it is usually called *p-nitrosophenol*, although the name *quinone monoxime* is also employed. It is a light-yellow, crystalline solid melting at 126°. It dissolves in organic solvents to furnish green solutions. It is a weak acid, and dissolves in aqueous alkali to form a brown solution of the sodium salt.

Preparation of Resorcinol. 1,3-Dihydroxybenzene, resorcinol, is prepared industrially by alkaline fusion of the corresponding disulfonic acid. Starting with benzene, the steps involved are the following:



It is also prepared by the fusion of meta bromobenzenesulfonic acid.

Ortho and para bromobenzenesulfonic acids and para benzenedisulfonic acid on fusion with alkali also yield resorcinol. Obviously, at the high temperatures of fusion, a rearrangement occurs. This fact is significant, since it demonstrates that fusion reactions are often unreliable in determining the structure of aromatic compounds.

Hexylresorcinol, $C_6H_3(OH)_2CH_2CH_2CH_2CH_2CH_2CH_3$ (1,3,4), (the numbers refer to the positions of the groups), is a derivative of resorcinol which has been found to have valuable antiseptic properties, and is now manufactured for this purpose.

Pyrocatechol. The ortho dihydroxybenzene, $C_6H_4(OH)_2$(1,2), is known as *pyrocatechol* or *catechol*. It can be prepared from ortho chloro-

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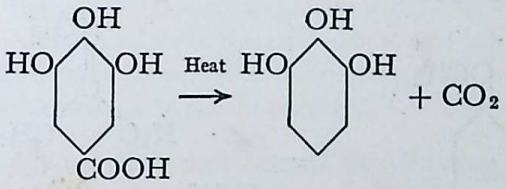
phenol by hydrolysis of the compound in an aqueous solution of sodium and strontium hydroxides in the presence of copper. It is easily oxidized in alkaline solution, yielding complex products. When oxidized with silver oxide under special conditions pyrocatechol yields ortho benzoquinone.

The pyrocatechol grouping occurs in a great variety of natural products; sometimes with both phenolic groups free, sometimes partially methylated, and sometimes combined with a methylene group. A number of such natural products, including the substance lignin present in wood, will be discussed in the following chapters.

Guaiacol, $C_6H_4(OCH_3)(OH)$ (1,2), is the monomethyl ether of catechol. It was first obtained by the destructive distillation of gum guaiacum (a resin), and occurs in large quantities in wood tar. It can be synthesized from phenol or benzene by a variety of processes. Guaiacol is a low-melting, colorless solid (mp 28°) with a characteristic, pleasant odor. It is used in medicine and pharmaceutical preparations. It can be converted into catechol by boiling with hydrobromic or hydriodic acid.

Pyrogallol from Gallic Acid. Pyrogallol, or pyrogallic acid, $C_6H_3(OH)_3$ (1,2,3), is one of the few aromatic compounds which is *not prepared from coal tar*. It has been synthesized from benzene in the laboratory, but the process is too difficult and expensive to be used industrially. **Gallic acid,** $C_6H_2(OH)_3COOH$, is a substance which is readily prepared from tannic acid (p. 506). On heating, gallic acid loses carbon dioxide and forms pyrogallol.



This trihydroxybenzene thus owes its importance to the fact that it can be readily obtained from a natural product (tannic acid). It is used as a developing agent and as a dye intermediate. Its alkaline solutions are very easily oxidized even by atmospheric oxygen. They are often used as an absorbent for oxygen in gas analysis.

Phloroglucinol. Symmetrical trihydroxybenzene, $C_6H_3(OH)_3$-1, 3,5, is called *phloroglucinol*. It may be prepared by the fusion of the sodium salt of 1,3,5-benzenetrisulfonic acid with sodium hydroxide. It is also prepared by fusing resorcinol with sodium hydroxide in air. In this reaction oxygen of the air is involved.

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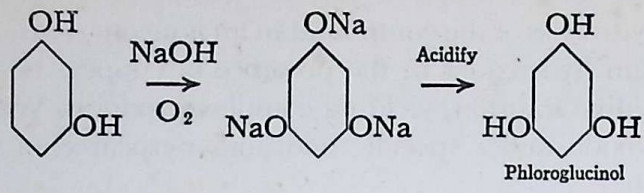
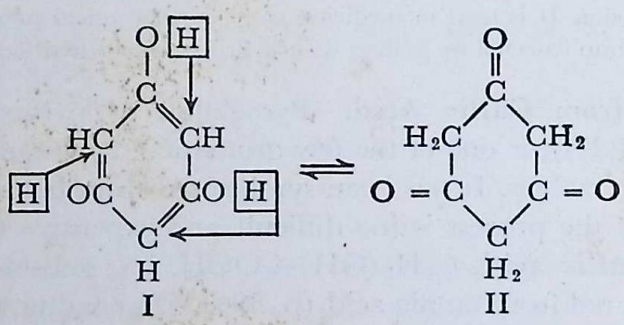
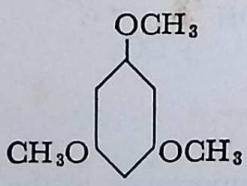


Phloroglucinol is a tautomeric substance; some of its reactions correspond to those expected from a trihydroxybenzene, while others indicate that it is a cyclic triketone. For example, when treated with diazomethane (p. 328), it forms a trimethyl ether; such a reaction is characteristic of the phenols. On the other hand, when treated with hydroxylamine it forms a trioxime. This latter reaction would seem to indicate that phloroglucinol was to be represented by formula II instead of I.

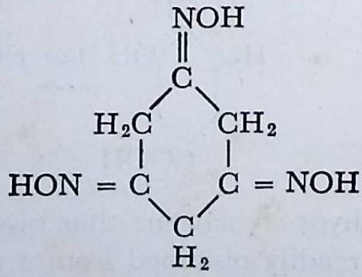


Trihydroxy formula of phloroglucinol

Triketo formula of phloroglucinol



Trimethyl ether of phloroglucinol; derived from phenolic form



Trioxime of phloroglucinol; derived from ketonic form

An inspection of the two tautomeric formulas I and II shows that I is the enolic form of II. We are evidently here concerned with the keto-enol tautomerism discussed in Chap. 14. No one has yet succeeded, however, in isolating isomeric forms of phloroglucinol corresponding to the two formulas. In solution or in the molten state both forms are probably present in equilibrium. There is no clear

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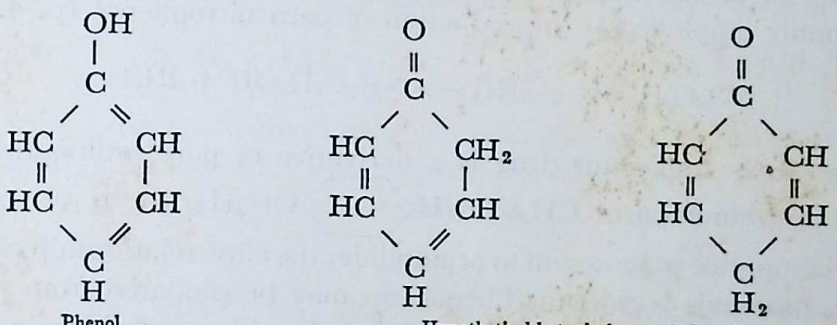
evidence to enable us to decide whether the solid is to be represented by formula I or II.

It is particularly interesting that the tautomeric shift of phloroglucinol involves the change from an aromatic structure to an alicyclic structure. This was also true of the tautomerism of nitrosophenol (quinone monoxime). It is evident that the distinction between aromatic compounds and alicyclic compounds may sometimes be bridged by a shift of one or more hydrogen atoms. The hydroxy derivatives of benzene are thus to be regarded as the enolic forms of certain alicyclic ketones. In the monohydroxy compounds (e.g., phenol), there is no evidence of the existence of any of the ketonic forms. Phenol, for example, does not form an oxime when treated with hydroxylamine. One of the most striking characteristics of aromatic compounds is that the hydroxyl derivatives are stable in the *enolic* form.



Phenol

Hypothetical ketonic forms of phenol

The alkylation of the potassium salt of phloroglucinol with methyl iodide takes place in somewhat the same manner as the alkylation of acetoacetic ester or malonic ester. The alkyl group becomes attached to carbon instead of oxygen. In this way a hexamethyl derivative of formula II can be prepared

Polyhydroxy Aromatic Compounds in Nature. The hydroxy derivatives of benzene are widely distributed in the plant world, often as glycosides (p. 289) in which the phenolic group is attached to a glucose or other sugar molecule. A number of more or less complicated substances derived from the polyhydroxy compounds are found in the tannins (p. 506). Pyrocatechol, hydroquinone, and phloroglucinol have been isolated as glucosides from many species of plants. The glucoside of hydroquinone, known as *arbutin*, is very common in the plant kingdom.

AMINOPHENOLS

The aminophenols are both aryl amines and phenols and give the characteristic reactions of both classes of substances. They are **am-**

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photeric like aluminum hydroxide, forming *salts with both acids and bases*. These salts are more soluble in water than the parent substances themselves.

$$\underset{\text{Soluble}}{NaOC_6H_4NH_2} \underset{NaOH}{\overset{HCl}{\rightleftharpoons}} \underset{\text{Only slightly soluble}}{HOC_6H_4NH_2} \underset{NaOH}{\overset{HCl}{\rightleftharpoons}} \underset{\text{Soluble}}{HOC_6H_4NH_2{\cdot}HCl}$$

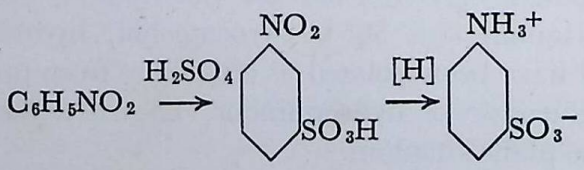
The solutions of the sodium salts are easily oxidized and are, therefore, not readily kept without change. The melting points of the three isomeric aminophenols are: ortho 170°, meta 123°, para 184°.

The Preparation of Para Aminophenol. This compound is important not only as a photographic developer but also as a dye intermediate, and is used in the synthesis of several drugs. There are a number of methods of preparing para aminophenol; the one most commonly employed is the reduction of para nitrophenol (p. 439).

$$NO_2C_6H_4OH + 6[H] \longrightarrow NH_2C_6H_4OH + 2H_2O$$

One fairly important drug is a derivative of para aminophenol. This is **phenacetin,** CH_3CONH OC_2H_5. It is an antipyretic superior in its action to acetanilide; the close relationship of the two compounds is evident. Phenacetin may be prepared from para aminophenol by ethylating the sodium salt with ethyl chloride and then acetylating the para ethoxy aniline (phenetidine) thus produced.

Meta Aminophenol. This compound is not used as a photographic developer but is a **dye intermediate.** Its preparation illustrates the general methods of obtaining meta compounds. The nitro group orients meta; therefore, if we introduce another substituent directly into nitrobenzene, a meta compound will be the product. On reduction we will then have a meta amino compound. **Metanilic acid,** $HO_3SC_6H_4NH_2$ (an isomer of sulfanilic acid), is prepared in this way.



The sodium salt of metanilic acid on fusion with sodium hydroxide and subsequent acidification of the reaction mixture, yields meta aminophenol.

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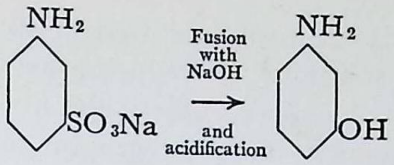
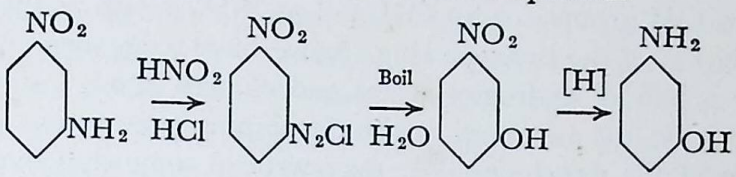
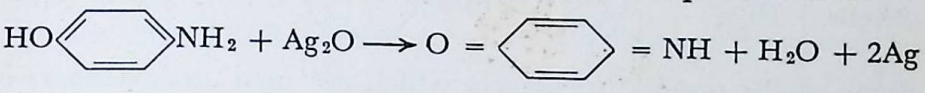


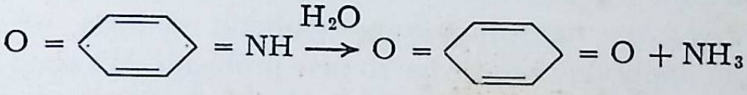
Another method of preparing meta aminophenol is from meta nitroaniline (p. 446). The amino group may be replaced by hydroxyl through the formation of the diazonium salt (p. 456). The meta nitrophenol is then reduced to the meta aminophenol.



Quinonimine. When para aminophenol is carefully oxidized by silver oxide, it loses two hydrogen atoms to form quinonimine.

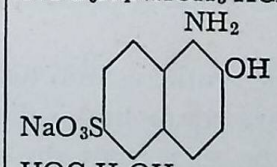


Like quinone-hydroquinone, quinonimine-aminophenol forms a reversible oxidation reduction system. Quinonimine is, however, very unstable. In the presence of dilute acids, it rapidly forms 1,4-benzoquinone.



Photographic Developers. A number of aminophenols and polyhydroxy derivatives of benzene are used as photographic developers.

PHOTOGRAPHIC DEVELOPING AGENTS

Scientific Name	*Formula*	*Trade Name*
p-Aminophenol hydrochloride	$HOC_6H_4NH_2 \cdot HCl$	Rodinal
p-Methylaminophenol sulfate	$HOC_6H_4NHCH_3 \cdot H_2SO_4$	Metol
2,4-Diaminophenol hydrochloride	$HOC_6H_3(NH_2)_2 \cdot HCl$	Amidol
p-Aminosaligenin hydrochloride	$HOC_6H_3(CH_2OH)NH_2 \cdot HCl$	Edinol
o-Methylaminophenol	$HOC_6H_4NHCH_3 \cdot HCl$	Ortol
Sodium 1-amino-2-naphthol-6-sulfonate		Eikonogen
Hydroquinone	HOC_6H_4OH	Hydroquinone
Pyrogallol	$HOC_6H_3(OH)_2$	Pyro

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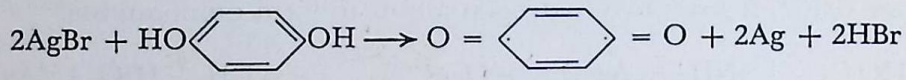
All these compounds are easily oxidized in alkaline solution. Therefore, their alkaline solutions are reducing agents and slowly reduce silver halide to metallic silver. This is the fundamental reaction involved in the development of a photographic plate, and these organic reducing agents are used widely as photographic developers. It is impossible to write equations representing the organic chemistry of this process as the oxidation products are complicated and numerous. In general, however, it may be noted that all the organic developers have two OH groups, or an OH and an NH_2 group in the ortho or para position of the benzene ring. As we have seen, such compounds can lose a pair of hydrogen atoms and change into a quinoid form. Undoubtedly, the first step in the developing process is a **dehydrogenation** of the developer. We may write a somewhat hypothetical equation for the first step as follows.



Some of the organic substances which are used as developers are given on p. 475. A few of these have already been discussed.

AROMATIC SYNTHESES

Having now considered a variety of classes of aromatic compounds and surveyed the more important synthetic methods, we are in a position to apply this knowledge to new problems. We shall illustrate such applications by outlining the synthesis of a few compounds. In working out synthetic problems in this branch of organic chemistry, the same general principles apply as in aliphatic chemistry (Chap. 8, p. 158). The chemist must have a knowledge of the various types of compounds and the more important general methods of synthesizing each. In aromatic chemistry, particular care must be taken to ensure that the proposed method will place the groups in the proper positions of the ring. The rules of orientation are here invaluable. The fundamental raw material is coal tar; from this the coal-tar crudes, benzene, toluene, the xylenes, phenol, naphthalene, and anthracene, can be isolated.

We may divide the syntheses into two groups according to whether (1) an ortho or a para compound is desired or (2) a meta compound is the goal. It will be seen from the examples below that even the synthesis of rather unusual derivatives of benzene is eventually based on a few well-known intermediates which are different in the two

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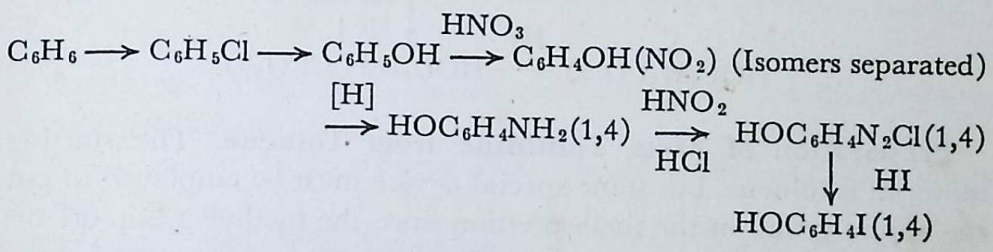
cases. As in aliphatic chemistry, one should endeavor to master the general principles and not attempt to commit the steps to memory. Each new problem should be solved by working out each step in the process *beginning with the last step.*

EXAMPLES OF THE SYNTHESIS OF A PARA COMPOUND

The Preparation of Para Iodophenol from Benzene. In outlining a solution of this problem, it is first recalled that an iodine atom cannot usually be directly introduced into the benzene ring; the diazonium replacement reaction, however, can be employed (p. 456). This requires a primary amine which in turn is prepared from a nitro compound. The hydroxyl group orients ortho and para, and, therefore, direct nitration puts the second group in the desired position.



The relative position of two or more groups should always be shown in each step either by numbers in parenthesis or, better, by writing the hexagonal formula.

The Preparation of Para Di-iodobenzene from Benzene. This problem is very similar to the first except that para nitroaniline is prepared (p. 448) instead of para nitrophenol. The diazotization of this amine and the replacement reaction yield para nitroiodobenzene. From this point the synthesis is identical with the one just outlined. Para nitroiodobenzene could also be formed by direct nitration of iodobenzene which in turn is prepared from aniline through the Sandmeyer reaction or by the action of nitric acid and iodine on benzene (p. 420). *Di-iodobenzene cannot be prepared from* $C_6H_4(NH_2)_2$ (see p. 464).

EXAMPLES OF META SYNTHESES

Meta Nitroaniline and Meta Aminophenol. These compounds are the basis of the synthesis of many meta compounds. The first is prepared either by the nitration of aniline (p. 446) or more usually by the partial reduction of meta dinitrobenzene. The reduction of

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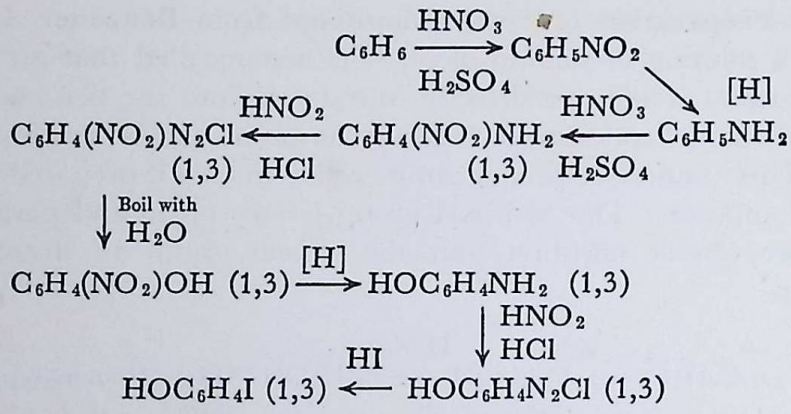
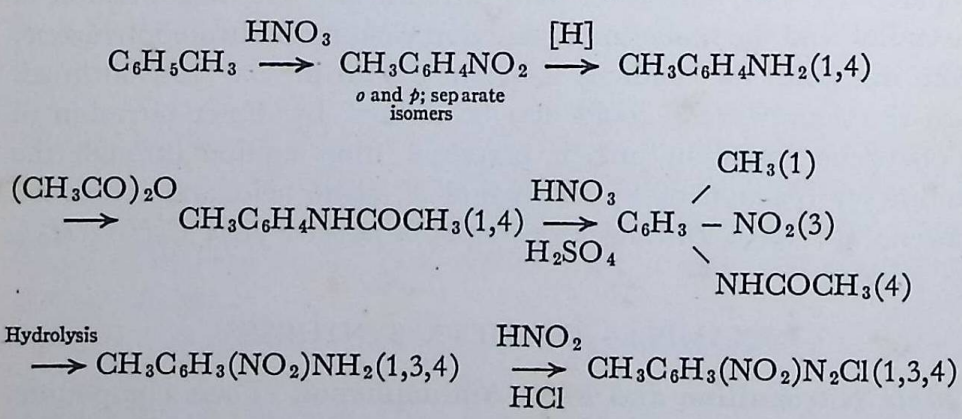
one nitro group of the dinitro compound is accomplished by using ammonium sulfide (p. 447). Two methods of preparing meta aminophenol have already been considered (p. 474).

The Preparation of Meta Iodophenol from Benzene. The steps in the solution of this problem are as follows:



Preparation of Meta Toluidine from Toluene. The starting material is toluene, but some special device must be employed to put the amino group in the meta position since the methyl group orients ortho and para. This is done by first introducing the acetylamino group in the para position, and subsequently removing it. Since the $NHCOCH_3$ group has a more powerful orienting influence than a methyl group (p. 424), the entering group takes the desired position. This is a very good illustration of the importance of a knowledge of the relative directing power of various groups. The steps are as follows:



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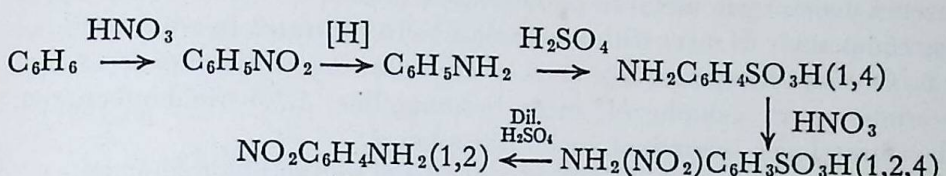
EXAMPLES OF ORTHO SYNTHESES

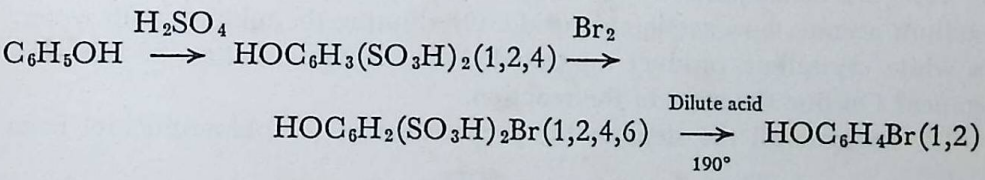
Under the illustrations of para syntheses, we have seen that in one step a mixture of ortho and para isomers is obtained. Generally, in designing a scheme for an ortho synthesis, the ortho isomer is separated and subjected to the necessary reactions. Sometimes the proportion of ortho isomer obtained is too small to be of preparative value, and then other methods must be devised. The following syntheses illustrate a method sometimes successful.

Preparation of Ortho Nitroaniline from Benzene.

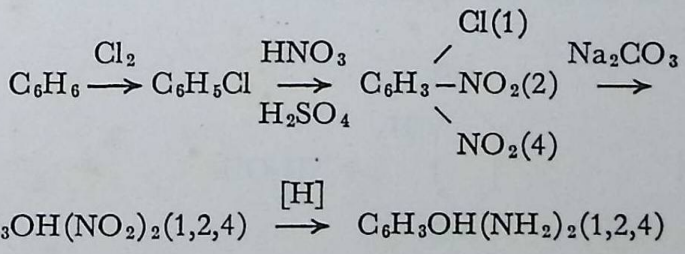


It should be noticed that the sulfonic acid group blocks the para position (sulfanilic acid), and, therefore, ortho substitution occurs. The sulfonic acid group is removed at the end by heating with dilute sulfuric acid (p. 427).

Preparation of Ortho Bromophenol. Since the monobromo compounds of phenol cannot be made directly, the ortho and para positions in phenol are blocked by sulfonic acid groups. On bromination the second ortho position is substituted.



Preparation of 2,4-Diaminophenol from Benzene. The industrial preparation of this compound (the photographic developer, amidol) illustrates how advantage may be taken of the reactive halogen in the nitro chlorobenzenes (nitro groups ortho and para). The steps in the synthesis are:



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QUESTIONS AND PROBLEMS

1. How is ortho phenylenediamine prepared? Write the equation for the reaction between the diamine and butane-2,3-dione.

2. What explanation can you suggest for the stability of phenol as compared with vinyl alcohol?

3. Write structural formulas for *p*-aminophenol hydrochloride, quinonimine, metanilic acid, phenacetin, and pyrogallol.

4. Compare the reactions of benzoquinone and mesityl oxide.

5. What characteristic of the diamines, amino phenols, and dihydroxybenzenes makes them useful as photographic developers? Would you expect these compounds to react with ammoniacal silver nitrate? In what way?

6. Outline the synthesis of each of the following compounds from coal tar crudes: para iodophenol, meta bromoaniline, 1,3,4-trichlorobenzene, ortho nitrotoluene, resorcinol, ortho nitrophenol.

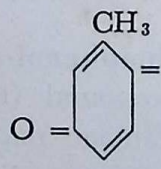
7. Discuss the tautomerism of nitrosophenol and of phloroglucinol.

8. How could you effect a chemical separation of *p*-$HOC_6H_4NHCH_3$, *p*-$HOC_6H_4NHCOCH_3$, and *p*-$CH_3NHC_6H_4CH_2OH$?

9. Write balanced equations for the following reactions: hydroquinone, methyl iodide, and alkali; *p*-nitrosodiethylaniline and alkali; benzenesulfonic acid and alkali; resorcinol and alkali; *p*-bromobenzenesulfonic acid and alkali. State the conditions under which each reaction is to be run.

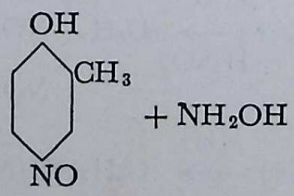
10. An organic compound is believed to be *p*-$BrC_6H_4NHCOCH_3$. Indicate the reactions you would use to prove this structure and show how you would synthesize the compound.

11. Para benzoquinone was allowed to react with a mixture of zinc dust, sodium acetate, and acetic anhydride. On diluting the mixture with water, a white crystalline product separated. What is the structure of this substance? Outline the steps of the reaction.

12. Indicate all the steps in the preparation of (*a*) phloroglucinol from toluene (*b*) 2,5-toluqinone, 

, from toluene, (*c*) orthobenzoquinone from benzene, (*d*) resorcinol from aniline.

13. It was found that the same product was obtained in the following reactions:

(*a*) 

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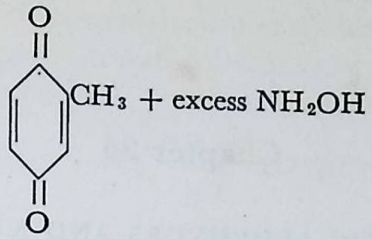
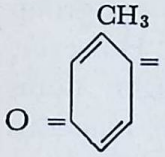
(*b*) 

Explain.

14. When ortho cresol was coupled with a benzenediazonium salt, a red solid was obtained. This substance on treatment with stannous chloride and hydrochloric acid gave a mixture of two colorless products, one of which was soluble in dilute alkali. When the latter was allowed to react with ferric chloride in dilute hydrochloric acid, the product obtained has the structure 

. Write the structure of the intermediates in this synthesis.

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Chapter 25

AROMATIC ALDEHYDES AND KETONES

AROMATIC ALDEHYDES

It is usual to limit the term *aromatic aldehyde* to those compounds in which the aldehyde group is directly attached to the aromatic nucleus. The aromatic aldehydes are similar in their carbonyl group reactions to the aliphatic aldehydes considered in Chap. 7. However, since the aromatic aldehydes do not contain alpha hydrogen atoms and do contain an aromatic nucleus, they differ in some reactions from the typical aliphatic aldehydes. These similarities and differences can best be illustrated by considering in detail the simplest aromatic aldehyde which is also the most important from the industrial standpoint.

Benzaldehyde, C_6H_5CHO. This aldehyde (bp 180°) is much used in the synthesis of compounds which contain aromatic groups. It is also employed as a perfume and flavoring material under the name of *oil of bitter almonds*. Before the development of the coal-tar dye industry it was prepared by crushing bitter almonds with water. These nuts contain a glucoside, **amygdalin,** and an enzyme which causes its hydrolysis to glucose, hydrocyanic acid, and benzaldehyde.

Benzaldehyde is now prepared industrially from toluene directly or from its chlorination products, benzyl chloride, $C_6H_5CH_2Cl$ or benzal chloride, $C_6H_5CHCl_2$ (p. 420).

The oxidation of toluene to benzaldehyde is brought about by the use of manganese dioxide and sulfuric acid with the addition of copper sulfate as catalyst.

$$C_6H_5CH_3 + [O] \xrightarrow[H_2SO_4]{MnO_2} C_6H_5CHO + H_2O$$

It is obvious that the production of an aldehyde by oxidation procedures must involve the use of special oxidizing agents and controlled conditions, as otherwise the aldehyde will be further oxidized to the corresponding acid.

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The conversion of benzyl chloride to benzaldehyde is accomplished by oxidation with an aqueous solution of lead or copper nitrates. Benzal chloride is readily transformed into benzaldehyde by boiling with water containing a small amount of alkali.

$$C_6H_5CH_2Cl + [O] \xrightarrow{Pb(NO_3)_2} C_6H_5CHO + HCl$$

$$C_6H_5CHCl_2 + H_2O \xrightarrow[CaCO_3]{100^\circ} C_6H_5CHO + 2HCl$$

The above methods are applicable to the preparation of other aromatic aldehydes from the corresponding methyl compounds.

Characteristics of Aromatic Aldehydes. Benzaldehyde and its derivatives are similar to those aliphatic aldehydes which have *no hydrogen in the alpha position*, for example, $(CH_3)_3CCHO$, and HCHO (cf. p. 149). They give the fuchsine test, reduce ammoniacal silver nitrate solution, combine with sodium bisulfite, hydrocyanic acid, and the Grignard reagent; they readily form oximes and phenylhydrazones.

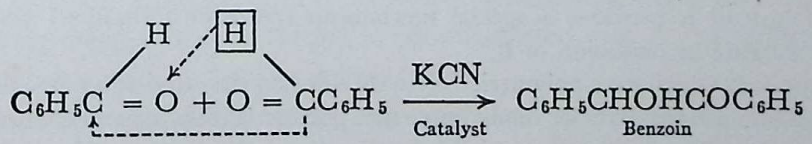
Because of the absence of an alpha hydrogen atom, they do not undergo an aldol condensation nor resinify when treated with alkali. Instead they undergo the Cannizzaro reaction (p. 149).

$$2C_6H_5CHO + NaOH \longrightarrow \underset{\text{Benzyl alcohol}}{C_6H_5CH_2OH} + \underset{\text{Sodium benzoate}}{C_6H_5COONa}$$

If a mixture of formaldehyde and an aromatic aldehyde is used, the formaldehyde is oxidized and the aromatic aldehyde is reduced. This reaction, known as a *crossed Cannizzaro reaction*, makes possible the reduction of aromatic aldehydes to the corresponding alcohols.

$$C_6H_5CHO + CH_2O + KOH \longrightarrow C_6H_5CH_2OH + HCOOK$$

A characteristic reaction of many aromatic aldehydes is the **benzoin condensation.** This is brought about by warming the aldehyde with a solution of potassium cyanide; the cyanide ion is the specific catalyst for this process. A graphical equation for the formation of benzoin, $C_6H_5CHOHCOC_6H_5$, from benzaldehyde will illustrate the reaction.



Unlike the aliphatic aldehydes, the aromatic aldehydes do not form polymers when treated with acids (cf. p. 131).

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Autooxidation. Benzaldehyde and certain of its derivatives absorb oxygen fairly rapidly when exposed to the air forming derivatives of hydrogen peroxide. Benzaldehyde itself forms **benzoyl hydrogen peroxide,** C_6H_5COOOH, or **perbenzoic acid.** The peroxide then oxidizes another molecule of benzaldehyde to benzoic acid. The process is called *autooxidation.*

$$C_6H_5CHO + O_2 \longrightarrow C_6H_5\overset{\overset{\displaystyle O}{\|}}{C} - O - OH$$

$$C_6H_5CHO + C_6H_5\overset{\overset{\displaystyle O}{\|}}{C} - O - OH \longrightarrow 2C_6H_5COOH$$

Although autooxidation is a common reaction, only from benzaldehyde has an intermediate peroxide been isolated; however, peroxide formation probably is a necessary step in all autooxidations. The reaction is autocatalytic; at the beginning the reaction is very slow and gradually it increases to a maximum velocity. The induction period (the time before the reaction is noticeable) indicates that either a certain concentration of peroxide must be formed before the rate becomes appreciable or minute amounts of impurities present as inhibitors must be removed. Generally autooxidations are very sensitive to catalysts, either positive or negative. Those of the latter class probably react with the intermediate peroxide and thus destroy it. Among such negative catalysts, which are called *antioxidants*, are those polyhydroxy compounds and aminophenols which are readily dehydrogenated by very mild oxidizing agents (Chap. 24). As little as 0.001 per cent of hydroquinone in benzaldehyde will prevent its autooxidation.

Quite frequently substances which are perfectly stable to oxygen are oxidized when added to a system capable of undergoing autooxidation. A general equation for an autooxidation may be written in which A is the substance which forms a peroxide AO_2, and B the substance which takes oxygen away from the peroxide (acceptor). The acceptor may be another molecule of A or another easily oxidized compound.

$$O_2 + A \longrightarrow AO_2 \qquad \text{peroxide formation}$$
$$AO_2 + B \longrightarrow BO + AO \qquad \text{peroxide oxidizes acceptor}$$

It often happens that the substance B (the acceptor) is not directly oxidized by atmospheric oxygen. The substance A (e.g., benzaldehyde) thus serves to bring about the indirect oxidation of B. This is another example of a *coupled reaction* (pp. 165, 389), the oxidation of A being coupled to that of B. Since both oxidations are exothermic the coupling does not serve to provide energy to an otherwise endothermic process; instead it provides a special mechanism (peroxide formation) which increases the rate of oxidation of B.

Compounds which may polymerize often do so when they undergo autooxidation, and peroxides are catalysts for many important polymerization processes. This probably means that the energy of the peroxide has been passed to a molecule of the substrate which is now in an active state ready either to combine with oxygen (autooxidation) or with another molecule (the first step in polymerization). The effect of

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peroxides on the addition of hydrogen bromide to ethylenic compounds (p. 59) is another example of a chain reaction. The discoloration and gum formation of cracked gasolines and the resinification of acrylic esters are catalyzed by autooxidation. The addition of small amounts of inhibitors is essential in storing these substances since the antioxidants prevent autooxidation and subsequent polymerization.

The drying of oil paints is another illustration of polymerization induced by autooxidation. Positive catalysts are often added to speed up the autooxidation process (quick-drying paints).

Side-Chain Compounds from Benzaldehyde. Compounds which contain an aromatic nucleus and a reactive group separated by a chain of carbon atoms are often called *side-chain compounds.* Many such substances can be synthesized with the aid of benzaldehyde. Substances which have a hydrogen in the alpha position to a carbonyl group react with benzaldehyde with the formation of *unsaturated side-chain compounds.* The reaction is brought about by acids or by bases. If acetaldehyde is used, **cinnamic aldehyde** is the product.

$$C_6H_5CHO + CH_3CHO \xrightarrow[\text{NaOH}]{\text{Dil.}} \underset{\text{Cinnamic aldehyde}}{C_6H_5CH = CHCHO} + H_2O$$

This aldehyde is a liquid which boils at 252°. It is a constituent of **oil of cinnamon** and has a pleasant cinnamon odor.

A similar condensation takes place between an aromatic aldehyde and a ketone containing the grouping $-CH_2CO-$. For example, benzaldehyde will condense with acetone forming an unsaturated ketone. Depending on the proportion of the reactants, **benzalacetone,** $C_6H_5CH = CHCOCH_3$, or **dibenzalacetone,** $(C_6H_5CH = CH)_2CO$, is formed.

$$C_6H_5CHO + CH_3COCH_3 \xrightarrow{\text{NaOH}} C_6H_5CH = CHCOCH_3 + H_2O$$

$$C_6H_5CHO + CH_3COCH = CHC_6H_5 \xrightarrow{\text{NaOH}} C_6H_5CH = CHCOCH = CHC_6H_5 + H_2O$$

Dibenzalacetone is a yellow, crystalline solid (mp 112°) which is easily isolated and identified in small quantities. The formation of dibenzalacetone is, therefore, recommended as a procedure for identifying small quantities of acetone.

The condensation reactions just described are obviously analogous to similar reactions in the aliphatic series discussed in Chap. 7. There is little doubt that an aldol (p. 137) is an intermediate product in each reaction.

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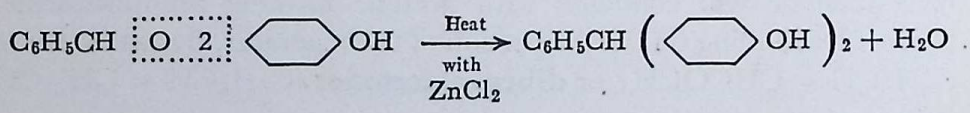
Perkin Reaction. Aromatic aldehydes will condense not only with aldehydes and ketones, but even with the sodium salts of aliphatic acids. This reaction is known as the *Perkin*[1] *reaction*, and is characteristic of aromatic aldehydes. As an example, we may cite the preparation of **cinnamic acid,** $C_6H_5CH = CHCOOH$. Acetic anhydride, sodium acetate, and benzaldehyde are heated together.

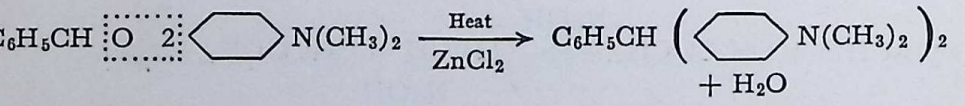
$$C_6H_5CHO + CH_3COONa + (CH_3CO)_2O \longrightarrow \underset{\text{Sodium cinnamate}}{C_6H_5CH = CHCOONa} + 2CH_3COOH$$

This reaction probably proceeds through an intermediate hydroxyl compound (analogous to an aldol), $C_6H_5CHOHCH_2COOH$, and, like the other similar condensations, the hydrogen atoms on the *alpha* carbon atom are involved. Thus, if sodium propionate and propionic anhydride are used, the product is $C_6H_5CH = C(CH_3)COOH$. Isobutyric acid, which has only one hydrogen on the alpha carbon atom, reacts with benzaldehyde to give a hydroxy acid or its lactone.

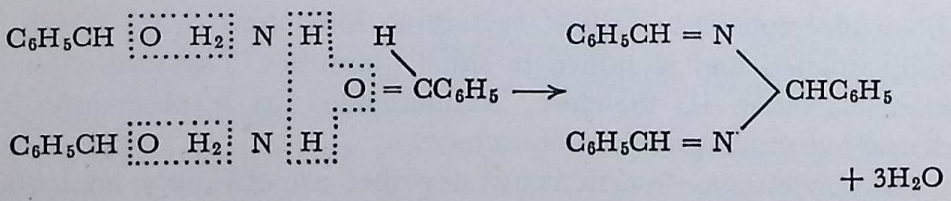
$$C_6H_5CHO + (CH_3)_2CHCOOH \longrightarrow C_6H_5CHOHC(CH_3)_2COOH$$

Certain Other Reactions of Benzaldehyde. Benzaldehyde and many of its derivatives will condense with those aromatic compounds which have an easily replaceable hydrogen atom in the para position. For example, phenol and dimethylaniline react with benzaldehyde according to the following equations; the reaction is useful in the synthesis of certain types of dyes.





The reaction between ammonia and benzaldehyde is complicated. Three molecules of the aldehyde and two of ammonia condense in the following manner.



The product is known as *hydrobenzamide*; it is a colorless solid melting at 110°.

[1] William Henry Perkin (1838–1907). Discoverer of the first coal-tar dyestuff, mauve, which he prepared while studying the action of oxidizing agents on crude aniline.

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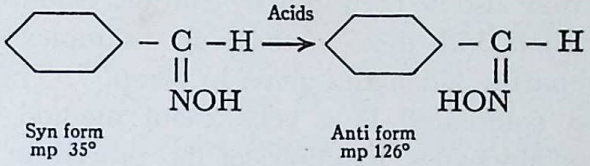
Isomeric Benzaldoximes. Two isomeric oximes can be prepared from benzaldehyde. The first product of the interaction of benzaldehyde and hydroxylamine is a crystalline solid which melts at 35°.

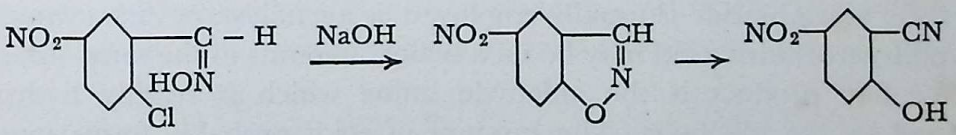
$$C_6H_5CHO + NH_2OH \longrightarrow \underset{\text{Benzaldoxime}}{C_6H_5CH = NOH} + H_2O$$

An isomeric substance melting at 126° is obtained by treating the low-melting oxime with hydrochloric acid. The two substances are geometrical isomers analogous to fumaric acid and maleic acid (p. 315).



The double linkage between carbon and nitrogen prevents free rotation, and two stereoisomers are possible depending on whether or not the hydroxyl group and hydrogen atom are over each other. This type of isomerism has been observed with the oximes of many aromatic aldehydes and ketones. Usually, in the aliphatic series only one form can be isolated. The terms *syn* and *anti* are used to designate the two forms of the aldoximes.

The configurations of the aldoximes were determined with the isomeric 2-chloro-5-nitrobenzaldoximes. Both isomers were treated with alkali. The higher melting isomer (obtained from the lower melting isomer by treatment with acid) lost hydrogen chloride to form an unstable cyclic compound; the lower melting isomer under the same conditions was unaffected. It was concluded from this that the higher melting isomer had the anti configuration (hydroxyl away from hydrogen and near the chlorine atom of the ring).



Anti (higher melting) forms nitrile readily with acetic anhydride

This conclusion was then generalized: the higher melting aldoximes, which are obtained from the lower melting isomers by treatment with acid, are assigned the anti configuration.

Pairs of isomeric aldoximes differ from each other in that one isomer, the anti, loses water more readily than the other to form a nitrile. Originally it was assumed that hydrogen and hydroxyl were nearer in the isomer which readily formed a

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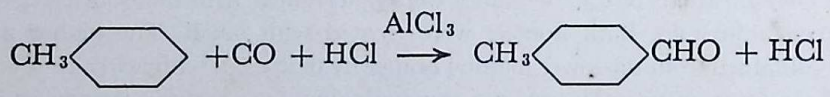
nitrile, and this reaction was used to assign configurations. We now believe that the loss of water from an aldoxime is not a simple process but takes place in steps between groups that are spatially distant.

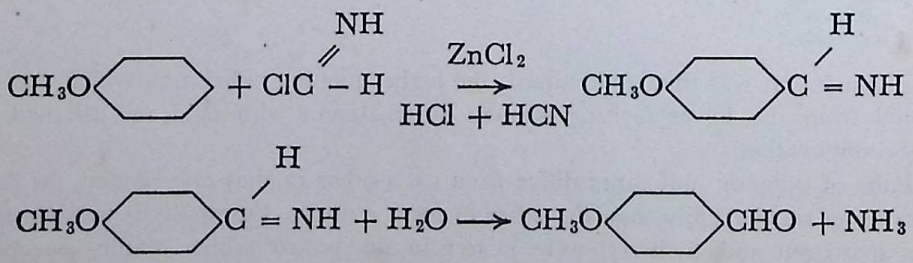
General Methods of Preparing Aromatic Aldehydes. In addition to the methods of preparing benzaldehyde mentioned at the beginning of this chapter, there are a few other general methods of importance.

Aromatic aldehydes can be prepared from the corresponding acids by distilling a mixture of the calcium salt with calcium formate (see p. 128). They may also be prepared by cautious oxidation of the corresponding alcohol. Both these methods are examples of the general methods of preparing aldehydes given in Chap. 7. The oxidation of an unsaturated compound is a very useful method of preparing certain aromatic aldehydes. Examples of this procedure will be given shortly (preparation of anisic aldehyde).

The aldehyde group may be directly introduced into the aromatic nucleus by two methods. The first may be illustrated by the preparation of *p*-methylbenzaldehyde (*p*-toluic aldehyde). It is really a modified Friedel-Crafts reaction (p. 410) since anhydrous aluminum chloride is the catalyst. A mixture of carbon monoxide and hydrogen chloride is employed which reacts as the equivalent of the unknown acid chloride of formic acid.



The second method of introducing the aldehyde group is employed with phenols and phenolic ethers. A mixture of hydrocyanic acid and hydrochloric acid is allowed to react with the phenol or phenolic ether; zinc chloride is usually employed as a catalyst, or zinc cyanide and hydrochloric acid may be used which amounts to the same thing. The first product is the aldehyde imine which is readily hydrolyzed to the aldehyde. The mixture of acids probably forms some HN = CHCl which then reacts with the aromatic compound.



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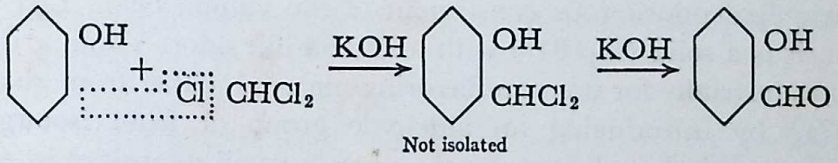
HYDROXY ALDEHYDES

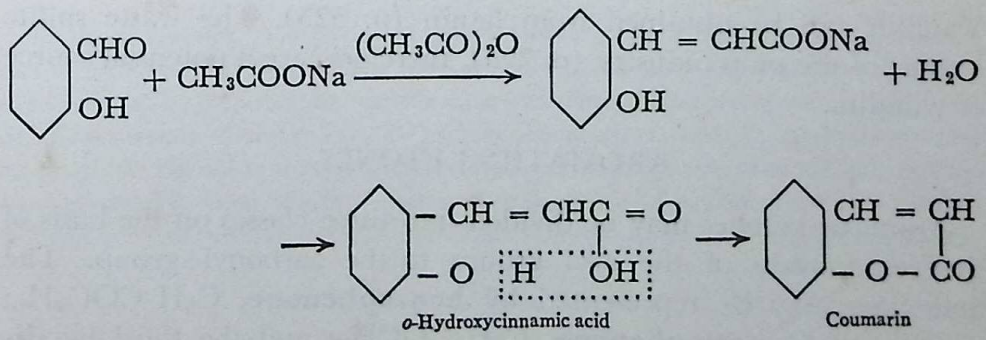
A number of hydroxy aldehydes and their ethers are important technically or are connected with interesting natural products. A few are used in the perfume industry.

Salicylaldehyde, HOC_6H_4CHO (1,2). The ortho hydroxybenzaldehyde is called *salicylaldehyde*. It occurs as a glucoside in a variety of plants. Salicylaldehyde is prepared by a reaction which can be employed for introducing the aldehyde group into *phenols*, and is known as the *Reimer-Tiemann* reaction. This consists in heating the phenolic substance with chloroform and potassium hydroxide; a mixture of ortho and para compounds results in which the ortho predominates. The first product of the reaction is probably a dichloride (an hydroxy benzal chloride), which is then hydrolyzed to an aldehyde. This hypothetical intermediate is shown in the equation below.



Salicylaldehyde is a colorless liquid boiling at 196° and solidifying at 1°. It has a pleasant odor.

Coumarin. Salicylaldehyde is manufactured as an intermediate in the synthesis of a substance of great importance in the perfume industry. This is coumarin, the inner lactone of **ortho hydroxycinnamic acid.** It is prepared by the Perkin reaction from salicylaldehyde, sodium acetate, and acetic anhydride. The sodium salt of ortho hydroxycinnamic acid is first formed; on liberating the free acid by acidification, water is immediately lost and the lactone ring is formed.



Coumarin is a colorless, crystalline solid which melts at 70°. It is

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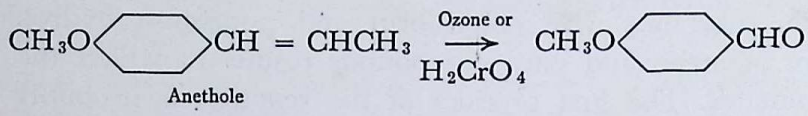
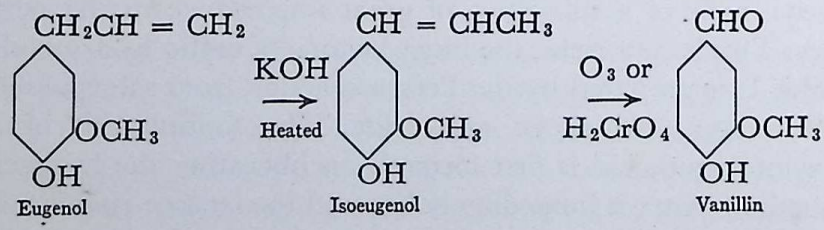
somewhat volatile, and has the odor of new-mown hay. Coumarin is widely distributed in nature usually as a glucoside; it occurs particularly in tonka beans from which it may be readily extracted. It is now prepared synthetically.

Ethers of Hydroxy Aldehydes. The methyl ether of para hydroxybenzaldehyde is known as *anisic aldehyde*, $CH_3OC_6H_4CHO$ (1,4). It is present in the essential oil from the anise seed. It is prepared industrially by oxidizing an unsaturated compound, **anethole,** which is the chief constituent of anise oil.



Anisic aldehyde boils at 248° and solidifies at 0°. It has a penetrating fragrant odor, and is used in the perfume industry.

Vanillin is a monomethyl ether of a dihydroxybenzaldehyde. It is the principal odoriferous constituent of the vanilla bean. Like coumarin, it is a solid (mp 81°) with a vanilla-like odor. Vanillin is prepared industrially for use as a flavoring material, either from guaiacol (p. 471) by introducing an aldehyde group or from **isoeugenol** by oxidation. Although isoeugenol occurs in small quantities in essential oils (e.g., nutmeg oil) it is prepared relatively cheaply by the rearrangement of **eugenol,** the chief constituent of **oil of cloves.** This rearrangement involves the shift of an ethylenic linkage.



Vanillin can be obtained from lignin (p. 523). The waste sulfite liquors of the pulp industry (p. 296), therefore, are a potential source of vanillin.

AROMATIC KETONES

Aromatic ketones may be divided into three classes on the basis of the relationship of the aryl groups to the carbonyl group. The first class may be represented by **benzophenone,** $C_6H_5COC_6H_5$; the second by **acetophenone,** $C_6H_5COCH_3$; and the third by **dibenzyl ketone,** $C_6H_5CH_2COCH_2C_6H_5$. The members of all three

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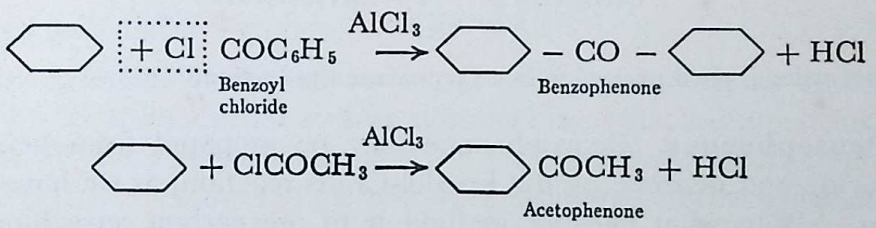
classes resemble the aliphatic ketones in most of their chemical properties. However, the immediate connection of an aryl group to a carbonyl group sets off the first two classes somewhat from the third, whose methods of preparation and whose reactions are those of the aliphatic ketones. We shall, therefore, consider a few representatives of the first two classes of ketones.

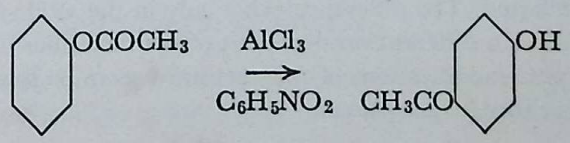
Methods of Synthesis. Aromatic ketones may be synthesized by most of the methods outlined in Chap. 7 for the preparation of aliphatic ketones: passing the vapors of the corresponding acids over metallic oxide catalysts, hydrolysis of dihalides, and oxidation of secondary alcohols.

In addition to these general methods of synthesizing aliphatic and aromatic ketones, there is one specific method for preparing aromatic ketones which contain the grouping $-ArCO-$. This is the Friedel-Crafts reaction using an acid chloride, anhydrous aluminum chloride, and an aromatic hydrocarbon. It may be illustrated by the preparation of benzophenone (diphenyl ketone) and acetophenone (phenyl methyl ketone).



The aluminum chloride is a catalyst in this reaction as in the alkylation of aromatic hydrocarbons (p. 414). However, 1 mole of the catalyst must be employed because it usually combines with the product to form a loose addition compound, and thus is removed continuously from the reaction.

Hydroxyketones. The hydroxyl derivatives of acetophenone and benzophenone can be prepared by the Friedel-Crafts reaction; but, since the presence of an hydroxyl group in the aromatic nucleus makes further substitution so much easier, less drastic procedures than the Friedel-Crafts reaction can be used. In the **Fries** reaction an ester of a phenol is treated with aluminum chloride; the acyl group shifts to the para or ortho position. Thus phenyl acetate dissolved in nitrobenzene and allowed to stand at room temperature with aluminum chloride forms *p*-hydroxyacetophenone.



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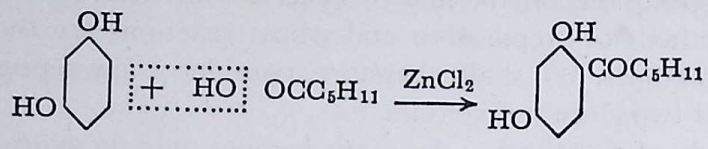
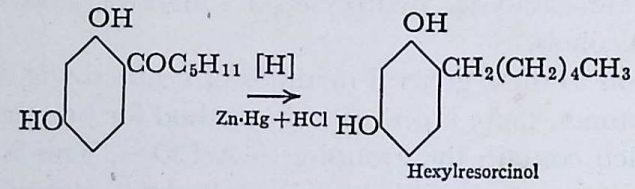
With *two* hydroxyl groups present the introduction of an acyl group is even easier, and it is only necessary to heat together the phenol, the acid, and zinc chloride. In this way resorcinol and caproic acid, $C_5H_{11}COOH$, yield resorcyl amyl ketone.



This substance can be used for preparing hexylresorcinol (p. 470), since the oxygen of the carbonyl group is replaced by hydrogen by reduction with amalgamated zinc and acid.



The reduction of the carbonyl group to the CH_2 group by this method is applicable to aromatic ketones; for example, acetophenone yields ethyl benzene.

$$C_6H_5COCH_3 \xrightarrow[\text{Zn·Hg + HCl}]{[H]} C_6H_5CH_2CH_3$$

This reaction is often referred to as a **Clemmensen reduction.**

Benzophenone. Benzophenone may be prepared from benzoyl chloride and benzene by the Friedel-Crafts reaction, as we have just seen. A somewhat cheaper method is to use carbon tetrachloride, benzene, and aluminum chloride. If the amounts of reactants and the conditions are carefully controlled, the interaction of the carbon tetrachloride and the benzene can be stopped after only two of the four halogen atoms have been replaced. The dichloride is then hydrolyzed to the ketone.

$$2C_6H_6 + CCl_4 \xrightarrow[5^\circ]{AlCl_3} \underset{\text{Benzophenone dichloride}}{C_6H_5CCl_2C_6H_5}$$

$$C_6H_5CCl_2C_6H_5 \xrightarrow{H_2O} C_6H_5COC_6H_5$$

Benzophenone exists in two solid modifications. One melts at 27°, the other at 48°. These two substances must have the same molecular structure, since on melting they give the same liquid. The difference exists only in the solid state, in solution it disappears; it is due to a different arrangement of the molecules in the crystal. Different crystallographic modifications of this sort are known as *polymorphic forms* and the phenomenon is called *polymorphism.*

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Benzophenone differs from most ketones in having no hydrogen atom on an alpha carbon atom. It will, therefore, not enter into condensation reactions which involve the removal of such an atom. In all other respects it is very similar in its reactions to acetone. It forms an oxime, is reduced to a secondary alcohol or a pinacol, and reacts with the Grignard reagent; it does not add sodium bisulfite. It is very resistant to oxidation.

Benzophenone and other aromatic ketones are cleaved when fused with potassium hydroxide. This reaction is useful in determining the structure of such compounds.

$$C_6H_5COC_6H_5 + KOH \xrightarrow{\text{Fused}} C_6H_6 + C_6H_5COOK$$

Acetophenone. This substance is the simplest example of a mixed aliphatic-aromatic ketone. Its preparation from acetyl chloride and benzene has been given above. In place of the acid chloride in this reaction the acid anhydride may be employed with somewhat better results. The aluminum chloride here definitely enters into the reaction since hydrogen chloride is evolved.

$$C_6H_6 + (CH_3CO)_2O + AlCl_3 \longrightarrow C_6H_5COCH_3 + CH_3COOAlCl_2 + HCl$$

Acetophenone is a liquid boiling at 202° and solidifying at 20.5°. Except for the fact that it does not combine with sodium bisulfite, it has all the characteristic chemical properties of a methyl ketone (p. 141). For example, it is readily brominated, forms chloroform when treated with alkaline sodium hypochlorite, and condenses with aldehydes. With selenium dioxide it is smoothly oxidized to phenyl glyoxal.

$$C_6H_5COCH_3 + SeO_2 \longrightarrow \underset{\text{Phenyl glyoxal}}{C_6H_5COCHO} + H_2O + Se$$

Benzalacetophenone, $C_6H_5CH = CHCOC_6H_5$. Benzaldehyde and acetophenone readily condense in the presence of dilute sodium hydroxide, forming an α,β-unsaturated ketone (p. 319), benzalacetophenone:

$$C_6H_5CHO + CH_3COC_6H_5 \longrightarrow C_6H_5CH = CHCOC_6H_5 + H_2O$$

Benzalacetophenone is a yellow, crystalline solid which melts at 58°. Its reactions are similar to those of benzalacetone (p. 485), mesityl oxide, and other α,β-unsaturated ketones.

Hydroxy Aromatic Ketones in Nature. A number of hydroxy aromatic ketones and their ethers are found in nature. Only a few of these are of sufficient interest to

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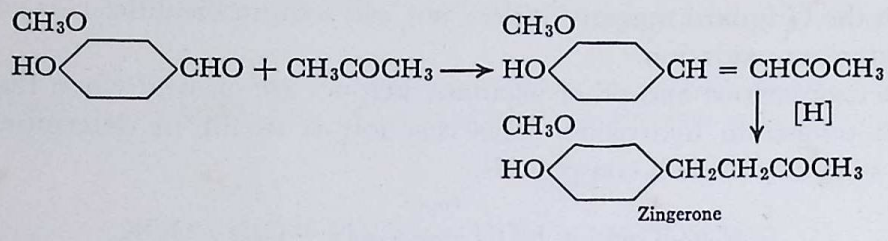
warrant consideration here. Among the simplest are ortho and para hydroxyacetophenones, $HOC_6H_4COCH_3$, which occur as glucosides isolated from certain trees. **Zingerone** is one of the constituents of ginger which imparts a biting taste to this material; it is 3-methoxy-4-hydroxybenzylacetone. The parent compound, **benzylacetone,** $C_6H_5CH_2CH_2COCH_3$, may be prepared by the catalytic reduction of benzalacetone (p. 485). In the same way zingerone may be synthesized from vanillin.



Benzoin and Benzil. The formation of benzoin from benzaldehyde has been discussed earlier in this chapter. Benzoin, $C_6H_5CHOHCOC_6H_5$, is a representative of the alpha hydroxy ketones or acyloins (p. 248). These substances are very easily oxidized to diketones. This oxidation or dehydrogenation may be brought about by complex cupric salts.

$$C_6H_5CHOHCOC_6H_5 \underset{[H]}{\overset{[O]}{\rightleftharpoons}} \underset{\text{Benzil}}{C_6H_5COCOC_6H_5}$$

The diketone, **benzil,** is easily reduced to benzoin. Benzoin is a colorless solid which melts at 137°; benzil is a yellow, crystalline material which melts at 95°.

In spite of the ease of the oxidation and reduction, a careful study of the relation of benzil to benzoin has shown that it is different from the relation of quinone to hydroquinone (p. 468). The processes of oxidation and reduction are not rapid enough to make the system strictly reversible; they proceed at a measurable rate. An electrode immersed in a mixture of benzoin and benzil does not take on a definite potential (cf. the quinone-hydroquinone system, p. 468).

Reduction of benzoin with sodium amalgam yields **hydrobenzoin,** a glycol. The reduction of benzoin with zinc and hydrochloric acid causes the replacement of the hydroxyl group by hydrogen. The product is phenyl benzyl ketone or **desoxybenzoin.**

$$C_6H_5CHOHCOC_6H_5 \xrightarrow[\text{NaHg}]{[H]} \underset{\text{Hydrobenzoin}}{C_6H_5CHOHCHOHC_6H_5}$$

$$C_6H_5CHOHCOC_6H_5 \xrightarrow[\text{HCl + Zn}]{[H]} \underset{\text{Desoxybenzoin}}{C_6H_5CH_2COC_6H_5}$$

When fused with potassium hydroxide, benzil undergoes a transformation known as the *benzilic acid rearrangement.* It involves the migration of a phenyl group.

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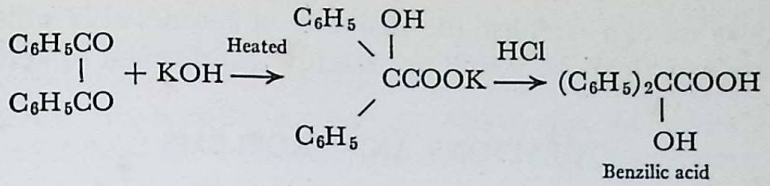
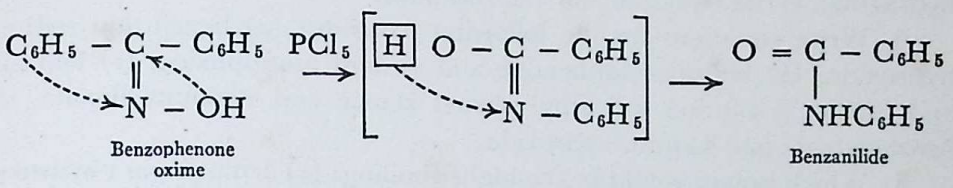
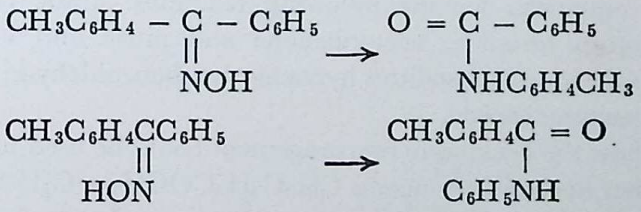


Structure of Ketones by Beckmann Rearrangement. When benzophenone oxime is treated with any one of a number of reagents, such as phosphorus pentachloride or acetyl chloride, a rearrangement to benzanilide (benzoyl aniline) occurs.



It should be noticed that the phenyl and hydroxyl groups trans (anti) to each other have changed places. We have purposely indicated this because it has been shown that a trans shift occurs by studying the rearrangement of ketoximes of established configuration. (The configurations were determined by methods similar to that shown for aldoximes on page 487.) When two isomeric ketoximes can be isolated each form gives its own substituted amide by a trans shift. This is illustrated by the rearrangement of the isomeric oximes of phenyl *p*-tolyl ketone.



The Beckmann rearrangement is probably the best example of the way, referred to earlier on page 206, in which intramolecular rearrangements can be used for establishing the structures or organic compounds. The substituted amide formed by the rearrangement is readily hydrolyzed to an amine and an acid. Identification of the amine and the acid establish the structure of the original ketone. Thus, from benzophenone through the oxime, rearrangement, and hydrolysis we obtain aniline and benzoic acid, C_6H_5COOH.

$$(C_6H_5)_2CO \longrightarrow (C_6H_5)_2C = NOH \longrightarrow C_6H_5NHCOC_6H_5 \longrightarrow C_6H_5NH_2 + C_6H_5COOH$$

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In this way we can establish the structure of ketones or of substances, like secondary alcohols, which are readily transformed to ketones.

QUESTIONS AND PROBLEMS

1. Write structural formulas for propiophenone, benzalacetophenone, benzyl phenyl ketone, benzoin, salicylaldehyde, coumarin, *p*-hydroxybenzophenone, benzil.

2. What product would you expect to obtain from benzoin and phenylhydrazine? Write equations for the reactions.

3. Write equations for the following reactions: (*a*) benzil and sodium hydroxide, (*b*) benzalacetophenone and sodium isopropoxide, (*c*) benzoin and Fehling's solution, (*d*) ethyl phenyl ketone and selenium dioxide, (*e*) benzaldehyde and sodium hydroxide.

4. Which isomer would be the higher boiling: (*a*) ortho or para hydroxyacetophenone? (*b*) salicylaldehyde or meta hydroxybenzaldehyde? Give the reasons for your answer.

5. How would you carry out the following transformations: (*a*) $(C_6H_5)_3CCOC_6H_5$ from benzophenone, (*b*) $CH_3CH_2CH_2CH_2C_6H_5$ from benzene and butyl alcohol (two methods), (*c*) $C_6H_5COCH_2Cl$ from benzene and acetic acid (two methods), (*d*) $C_6H_5CHBrCH_2COOH$ from benzaldehyde and acetic acid?

6. What is the Reimer-Tiemann reaction? What product would you expect to obtain if you substituted carbon tetrachloride for chloroform in this reaction?

7. Write equations for the following reactions: anisic aldehyde and phenylmagnesium bromide, acetophenone and nitric and sulfuric acids, *p*-bromoacetophenone and sodium hypochlorite, benzaldehyde and aqueous alcoholic potassium cyanide.

8. Show how the Beckmann rearrangement could be used in order to determine whether a certain ketone was $CH_3C_6H_4COCH_3$ or $C_6H_5COCH_2CH_3$.

9. Starting with vanillin, how would you synthesize 3,4-dimethoxybenzophenone?

10. What is the explanation for the existence of pairs of isomeric aldooximes? How are configurations assigned to the aldoximes?

11. Outline the general methods of synthesizing aromatic aldehydes, giving an example of each method.

12. Compare the autooxidation of benzaldehyde and acetaldehyde.

13. By what chemical test would you distinguish between $CH_3OC_6H_4CH_2COC_6H_5$, $CH_3C_6H_4CHOHCOC_6H_5$, and $HOC_6H_4CH_2CH_2COC_6H_5$?

14. Predict the product of the reaction between benzalacetophenone and ethylmagnesium bromide,

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15. How many products would you expect to obtain by adding bromine to benzalacetophenone? Would they be optically active?

16. Write the structure of the product you would obtain from the following reactions: (*a*) benzene, succinic anhydride, and aluminum chloride; (*b*) phenacyl bromide (α-bromoacetophenone) and the sodium salt of malonic ester; (*c*) benzilic acid and boiling hydriodic acid; (*d*) benzaldehyde and aniline.

17. Discuss briefly the isomerism of aromatic oximes. How many isomeric oximes of benzil are possible?

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Chapter 26

AROMATIC ACIDS: PHTHALEINS: RESINS AND PLASTICS

We shall consider in this chapter those acids in which a carboxyl group is directly joined to an aromatic nucleus or removed by one or more carbon atoms. On the whole, these acids differ less from the corresponding aliphatic compounds than do any other class of aromatic substances. For this reason, most of the chemical properties need be but briefly discussed. Three aromatic acids (benzoic, salicylic, and phthalic) are of industrial importance because they are used as intermediates in the preparation of dyes, drugs, and solvents. A number of aromatic acids and their derivatives occur in nature, and one large class of tannins is composed of condensation products of a trihydroxybenzoic acid.

COMPOUNDS WITH DIRECT UNION OF ARYL AND CARBOXYL GROUPS

General Methods of Preparation. The methods of preparing aromatic acids of the general formula, ArCOOH, may be illustrated by the preparation of benzoic acid, C_6H_5COOH. With certain exceptions, the same methods may be used for the preparation of a great variety of substituted benzoic acids and may, therefore, be considered as general methods. The preparation of aromatic acids by oxidation of the corresponding aldehyde (directly or indirectly by the Cannizzaro reaction) was considered in the last chapter and need not be repeated here.

1. Transformation of a side chain to COOH.

This can often be accomplished by direct oxidation if the molecule contains no other groups which are sensitive to oxidation.

$$C_6H_5CH_2CH_3 + [O] \longrightarrow C_6H_5COOH + 2H_2O + CO_2$$

2. Replacement of $-SO_3Na$ by $-COOH$.

Fusion of a sodium aryl sulfonate with sodium cyanide yields an aromatic nitrile, which may be then hydrolyzed to the acid.

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$$C_6H_5SO_3Na + NaCN \xrightarrow{\text{Fuse}} C_6H_5CN \xrightarrow{\text{Hydrolyze}} C_6H_5COOH$$

3. Replacement of $-NH_2$ by $-COOH$.

A primary amine is diazotized, converted to a nitrile (p. 457), which is hydrolyzed.

$$C_6H_5NH_2 \xrightarrow[HNO_2]{HCl} C_6H_5N_2Cl \xrightarrow{CuCN} C_6H_5CN \xrightarrow{\text{Hydrolyze}} C_6H_5COOH$$

4. The use of a Grignard Compound.

In this method an aryl halide is prepared, allowed to react with magnesium, and the organomagnesium compound treated with carbon dioxide. Obviously the method is not applicable if the molecule cannot be halogenated, or if it contains groups which react with the Grignard reagent (e.g., the carbonyl group or groups with an active hydrogen).

$$C_6H_5Br \xrightarrow{Mg} C_6H_5MgBr \xrightarrow{CO_2} C_6H_5COOMgBr \xrightarrow{H_2O} C_6H_5COOH$$

General Characteristics of Aromatic Acids. Although benzoic acid and its alkyl and halogen derivatives resemble the aliphatic acids in chemical properties, their physical properties are different. We proceed therefore somewhat differently in handling aromatic acids. For example, we prepare the free acid from the salt, not by distilling with sulfuric acid, but merely by acidifying a fairly concentrated solution of the soluble salt. Almost all the aromatic acids are insoluble in water, and at once precipitate when a water solution of their salts is treated with a strong acid.

Esters, acid chlorides, and acid anhydrides of aromatic acids can be prepared by the reactions used in aliphatic chemistry. On heating with sodium hydroxide, sodium benzoate forms benzene.

$$C_6H_5COONa + NaOH \xrightarrow{\text{Heat}} C_6H_6 + Na_2CO_3$$

The ortho and para hydroxybenzoic acids lose carbon dioxide much more readily, simply by heating the free acids. The preparation of pyrogallol is an illustration of this reaction (p. 471).

Benzoic Acid. This acid is a white, crystalline solid, melting at 122°, and is slightly soluble in water, easily sublimed, and volatile with steam. It occurs in the natural resin, gum benzoin, and in small amounts in cranberries. It is prepared on a large scale by hydrolysis

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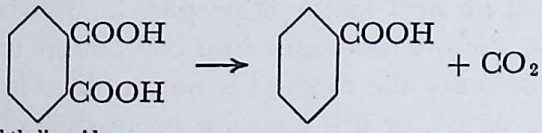
of **benzotrichloride,** $C_6H_5CCl_3$, which is obtained by chlorinating toluene (p. 420).

$$2C_6H_5CCl_3 + 4Ca(OH)_2 \xrightarrow{\text{Boil}} (C_6H_5COO)_2Ca + 3CaCl_2 + 4H_2O$$

$$(C_6H_5COO)_2Ca + 2HCl \longrightarrow 2C_6H_5COOH + CaCl_2$$

Since benzoic acid is nearly insoluble in cold water, acidification of an aqueous solution of the salt produces a precipitate of the acid.

Benzoic acid is also manufactured by the catalytic decomposition of phthalic acid (p. 507) in the presence of steam. One carboxyl group is removed during this process.



Phthalic acid

Toluene, benzyl chloride, ($C_6H_5CH_2Cl$) (p. 420), and a number of other substances can be oxidized to benzoic acid. The oxidation of toluene in the vapor phase by means of some inorganic oxide has been developed as an industrial method of preparation. Some benzoic acid has been prepared industrially by the oxidation of benzyl chloride with dilute nitric acid. .

Benzoyl Chloride. The acid chloride of benzoic acid, benzoyl chloride, C_6H_5COCl, may be prepared in the usual way from benzoic acid and phosphorus pentachloride. It can also be prepared by a reaction which is peculiar to the aromatic series and which consists in chlorinating benzaldehyde.

$$C_6H_5C(H)=O + Cl_2 \longrightarrow C_6H_5C(=O)-Cl + HCl$$

Benzoyl chloride is a liquid which solidifies at $-1°$ and boils at 198°. It has an acrid, irritating odor.

Benzoyl chloride is insoluble in water and reacts with it only slowly. In the presence of aqueous sodium hydroxide, it reacts with a variety of amino and hydroxyl compounds forming benzoyl derivatives. These derivatives are oftentimes solids of low solubility in water, and the reaction is used to prepare characteristic solid derivatives of alcohols and amines. The process is known as the *Schotten-Baumann reaction;* benzoyl chloride is shaken with an aqueous sodium hydroxide solution of the hydroxy or amino compound.

$$C_6H_5COCl + ROH + NaOH \longrightarrow C_6H_5COOR + NaCl + H_2O$$

$$C_6H_5COCl + RNH_2 + NaOH \longrightarrow C_6H_5CONHR + NaCl + H_2O$$

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Benzoyl Peroxide. A very interesting compound, which finds use as a catalyst for many polymerization reactions, can be readily prepared by the action of benzoyl chloride on sodium peroxide.

$$2C_6H_5COCl + Na_2O_2 \longrightarrow C_6H_5\overset{\overset{\displaystyle O}{\|}}{C} - O - O - \overset{\overset{\displaystyle O}{\|}}{C} - C_6H_5 + 2NaCl$$

Benzoyl peroxide (also known as *dibenzoyl peroxide*) is a colorless, crystalline solid which melts at 103°. It is a derivative of hydrogen peroxide (HOOH), in which both hydrogen atoms have been replaced by acyl groups. When it is treated with sodium ethoxide one benzoyl group is eliminated. The product is the sodium salt of monobenzoyl hydrogen peroxide or **perbenzoic acid.**

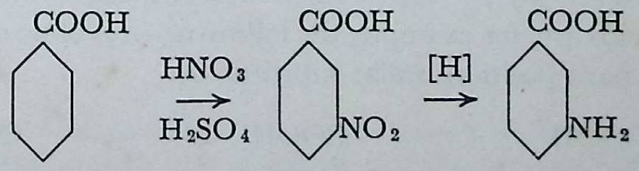
$$(C_6H_5CO)_2O_2 + NaOC_2H_5 \longrightarrow C_6H_5COOC_2H_5 + C_6H_5\overset{\overset{\displaystyle O}{//}}{C} - O - ONa$$

$$C_6H_5\overset{\overset{\displaystyle O}{//}}{C} - O - O - Na + H_2SO_4 \xrightarrow{\text{Cold}} \underset{\text{Perbenzoic acid}}{C_6H_5\overset{\overset{\displaystyle O}{//}}{C} - O - O - H} + NaHSO_4$$

Unlike dibenzoyl peroxide, benzoyl hydrogen peroxide is unstable. It is a powerful oxidizing agent. It reacts with ethylene derivatives, adding one atom of oxygen to the double linkage forming an ethylene oxide derivative. It will be recalled that benzoyl hydrogen peroxide is the reactive intermediate in the autooxidation of benzaldehyde (p. 484).

Derivatives of Benzoic Acid. The carboxyl group directs a second substituent into the meta position. It is, therefore, easy to prepare meta derivatives of benzoic acid or its esters by direct nitration, sulfonation, or halogenation. Substituted benzoic acids containing groups in the ortho or para position are usually synthesized by first preparing the corresponding ortho or para substituted toluene and then converting this to the corresponding acid by oxidation.

Nitro- and Aminobenzoic Acids. The nitration of benzoic acid yields meta nitrobenzoic acid from which by reduction the meta aminobenzoic acid is formed.



The para aminobenzoic acid can be prepared by the reduction of para nitrobenzoic acid which is formed by the oxidation of para nitrotoluene.

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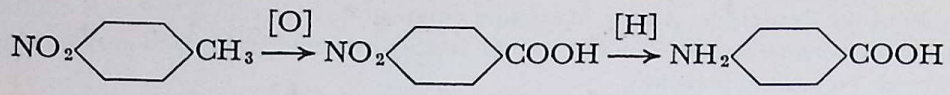
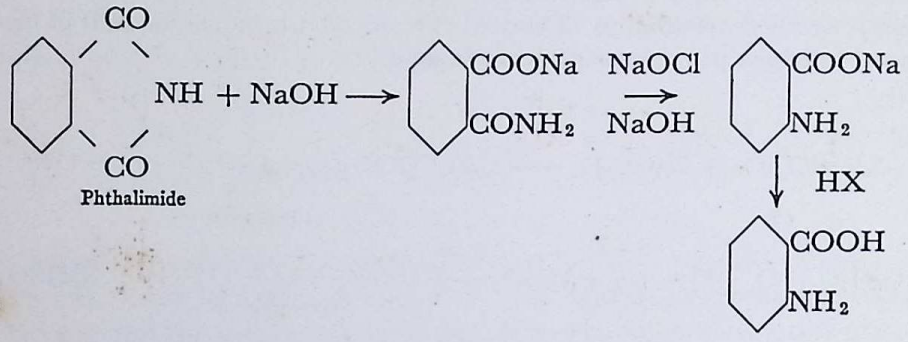


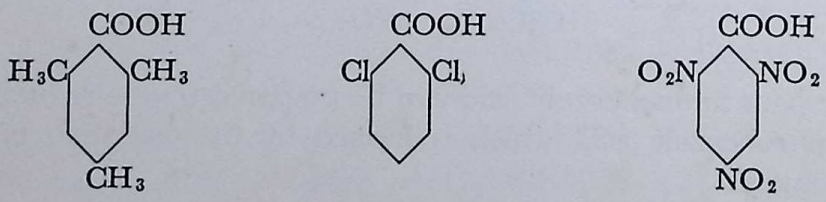
The ortho aminobenzoic acid is known as *anthranilic acid*. It is prepared by the action of alkaline sodium hypochlorite on phthalimide (the Hofmann reaction, p. 180). The first step in this reaction is probably an hydrolysis by which the ring is opened and an amide is formed.



All three aminobenzoic acids are colorless, crystalline solids slightly soluble in water. They are amphoteric substances forming salts with acids or bases. The meta and ortho compounds are used in the preparation of certain dyes (the latter was formerly employed in the synthesis of indigo); para aminobenzoic acid in the form of its esters is used as a local anesthetic (see novocain, p. 632). The **methyl ester of anthranilic acid** occurs in certain essential oils, and is manufactured for use in the perfume industry. Its odor is reminiscent of grapes.

Toluic Acids, $CH_3C_6H_4COOH$. The three methyl benzoic acids can be made by the partial oxidation of the three isomeric xylenes. Dilute nitric acid is generally used as the oxidizing agent. They are all solids; the ortho melting at 104°, meta at 110°, and para at 179°.

Esterification of Ortho Substituted Acids. Derivatives of benzoic acid which contain two substituents in the ortho position are peculiarly difficult to esterify by the direct method of heating with alcohol and acid. Such acids are, for example, the following (it is of no consequence whether the para position is also substituted).



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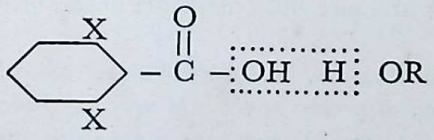
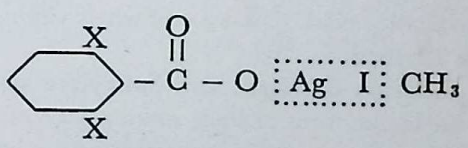
The esters may be readily prepared, however, by treating the silver salt with methyl iodide (p. 92). When formed, the esters are hydrolyzed only very slowly.

These facts are similar to the behavior of tertiary acids and tertiary alcohols, which was mentioned in Chap. 5 (p. 97). In the aromatic acids substitution in the ortho position (but not in the meta or para) has an effect equivalent to substitution in the alpha position in the aliphatic series. It is significant that either a methyl group or a nitro group will suffice to retard the reaction, although these two groups are very different in many respects (e.g., their effect on the basic strength of amines, p. 188). This suggests that the effect may be due to the spatial bulk of the group rather than its influence through the ring on the carboxyl group. Such an explanation supposes that the esterification of ortho substituted aromatic acids and highly substituted aliphatic acids is retarded by spatial interference of the substituents. One may imagine that the approach of the alcohol group to within the sphere of influence of the carboxyl group may be hindered. Such an effect has been called *steric hindrance* by the advocates of this theory. The fact that the esters may be formed through the silver salt may be readily explained by the theory. This reaction does not involve a group directly attached to the carbonyl group; it is one atom removed in space from the blockading groups and hence can proceed without interference.

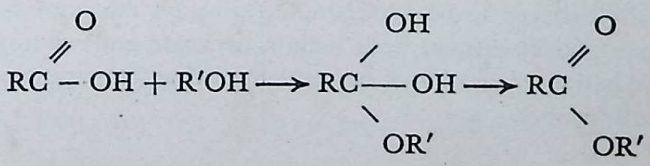


X retards reaction



X does not retard reaction

According to one theory of esterification, the first step in the process is the addition of a molecule of alcohol to the carbonyl group of the carboxyl group. The resulting derivative of the ortho form then loses water forming the true ester.



If this is the mechanism, the "steric hindrance" applies to the first step in the process. Indeed, it is found that the rate of addition reactions of aromatic aldehydes and ketones is tremendously decreased by ortho substitution. It will be noted that esterification through the silver salt could not involve an addtion reaction of the carbonyl group.

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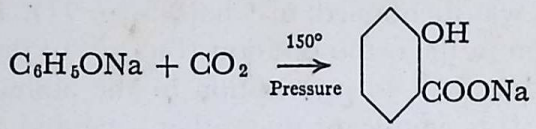
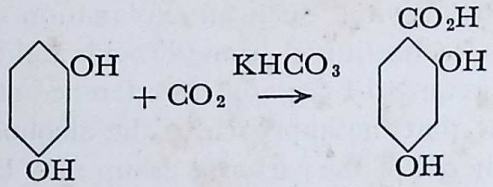
Salicylic Acid, $C_6H_4(OH)COOH(1,2)$. This hydroxy acid is a solid melting at 159°; it is more soluble in water than is benzoic acid. Sodium salicylate is prepared by a very remarkable reaction called the Kolbe [1] synthesis which is illustrated by the following equation.



An intermediate phenol carbonate, $C_6H_5OCO_2Na$, is first formed; this then undergoes rearrangement.

The comparable reaction between resorcinol and bicarbonate ion to form β-resorcylic acid takes place in aqueous solution at



atmospheric pressure.

The energy relations and the equilibria in carboxylation and decarboxylation reactions have already been referred to (p. 224 and p. 397). The energy relations in the hydroxy aromatic acids are not very different from those in the aliphatic acids, but the **rates** of both the addition of carbon dioxide under alkaline conditions and the loss of carbon dioxide from the free acids are greater with the hydroxy aromatic acids. This is a case where changes of structure affect markedly the **mobility** of a system.

Sodium Benzoate and Salicylate as Preservatives. Benzoic acid and salicylic acid in the form of their sodium salts are used as preservatives and very mild antiseptics. Enormous quantities of sodium benzoate are used each year in the preserving of fruits and vegetables, and in the manufacture of "ketchups." The legend "preserved with one tenth of one per cent of benzoate of soda" is probably familiar to all who have had occasion to scrutinize the labels on cans of preserved products. Sodium salicylate is used to a less extent. Sodium benzoate in the quantities used in preserving foods is generally believed to be noninjurious, although this has been a subject of some controversy and discussion. Both sodium benzoate and sodium salicylate are extensively used in the preparation of antiseptic medicinal preparations, such as tooth pastes and mouth washes.

MEDICINAL PRODUCTS FROM SALICYLIC ACID

The chief use of salicylic acid is in the preparation of three compounds of great medicinal importance: salol, aspirin, and methyl

[1] Hermann Kolbe (1818–1884), professor of chemistry at the University of Leipzig.

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salicylate. Sodium salicylate itself has valuable medicinal properties, particularly in treating rheumatism. However, when taken through the mouth it is very largely absorbed in the stomach, and this often leads to unpleasant symptoms. Chemists early endeavored to modify the salicylic acid molecule in some way so that these unpleasant effects would be overcome.

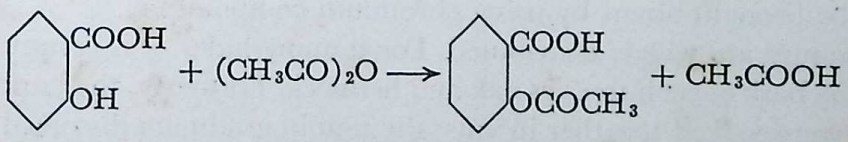
Salol. By esterifying salicylic acid with phenol the phenyl ester known as salol can be prepared.

$$3C_6H_4(OH)COOH(1,2) + 3C_6H_5OH + POCl_3 \xrightarrow{120^\circ} 3C_6H_4(OH)COOC_6H_5 + H_3PO_4 + 3HCl$$

It should be noted that, since salol is an ester of phenol, it cannot be prepared by the usual esterification method; a special procedure involving phosphorus oxychloride and a relatively high temperature is employed.

Salol, being an ester, passes unchanged through the stomach, which is acid, but is hydrolyzed in the intestines, which are alkaline. Phenol and salicylic acid are there liberated and absorbed. Salol is, therefore, a powerful intestinal antiseptic and is widely used as such. It is also employed as a coating for medicinal pills whose content is effective only if liberated in the intestines. Such pills pass through the stomach intact but disintegrate in the intestine. Salol is a crystalline solid melting at 42°.

Aspirin, $C_6H_4(OCOCH_3)COOH(1,2)$. This is another salicylic acid derivative, one of the most familiar of all coal-tar products. It is made by the acetylation of the phenolic group in salicylic acid.



Aspirin is a colorless solid melting at 134°; it is insoluble in water. Its physiological action is probably due to the fact that it is hydrolyzed in the intestines, liberating salicylic acid which is there absorbed by the system. Aspirin has become a popular remedy for all complaints. Almost 9,500,000 lbs, the equivalent of more than 13,000,000,000 five-grain tablets, were manufactured in the United States in 1944.

Methyl Salicylate, $C_6H_4(OH)COOCH_3$. This ester occurs in certain plants and is the chief constituent of oil of wintergreen. It is a colorless liquid which boils at 224° and has a pleasant wintergreen odor. It is made synthetically by esterifying salicylic acid in the usual

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manner with methyl alcohol. It is widely used in the flavoring industry and in the preparation of liniments and similar remedies for aches, sprains, and bruises. Methyl salicylate has the rather unusual property of penetrating the skin when rubbed on the surface. Probably hydrolysis takes place when the ester has penetrated, and the liberated salicylic acid has some physiological action which relieves the local pain.

GALLIC ACID AND TANNINS

Gallic Acid, $C_6H_2(OH)_3COOH$ (3,4,5-trihydroxybenzoic acid). Gallic acid is prepared by the hydrolysis of **tannins.** *It is not a coal-tar product.* It is a solid soluble in water and crystallizes from the aqueous solution with a molecule of water of crystallization, which it loses on heating. When heated above 200°, it loses carbon dioxide and forms pyrogallol (p. 471).

Tannins. A group of substances of vegetable origin have long been known as the *tannins.* They are amorphous powders, soluble in hot water and also in ether. Their solutions have a very astringent taste and are colored dark blue-black or greenish by the addition of ferric salts. This latter fact has led to the extensive use of tannins in the manufacture of writing inks. Tannins react with **proteins** (Chap. 19); if the protein is soluble, as is gelatine or white of egg, a voluminous precipitate is formed on adding a solution of a tannin. Insoluble proteins, such as the hide of animals, are changed by immersion in tannin solutions and the product is leather. The tanning of hides can also be brought about by using chromium compounds.

Tannins are widely distributed. For tanning hides, it is common to use the bark of such trees as oak and hemlock. Formerly, the bark and hide were soaked together in vats; the tannin gradually dissolved and acted on the protein material. The more modern practice uses extracts of vegetable material rich in tannins. Solutions of these extracts are prepared and used in treating the hides.

Gallotannin. The usual **tannic acid** of commerce is gallotannin. This is obtained principally from gallnuts, which are excrescences formed by the sting of insects on the branches of certain species of oak. Tannic acid is extracted from the powdered material with hot water. This material is used as a mordant in dyeing cotton cloth with basic dyes and also in the manufacture of inks. The commerical material may be further purified by extraction with ether or ethyl

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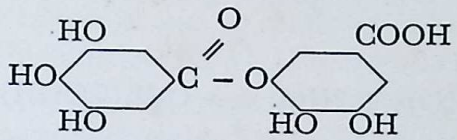
acetate; the tannin dissolves and is obtained by evaporation. Tannic acid is used in medicine as an astringent and for treatment of burns.

The study of carefully purified gallotannin has shown that it is a material of *high molecular weight*, which on hydrolysis with dilute sulfuric acid yields gallic acid and glucose. The relative amounts of the products as well as the general behavior of the tannin itself point to the following formula:

$$C_6H_7O[C_6H_2(OH)_3COOC_6H_2(OH)_2COO]_5$$

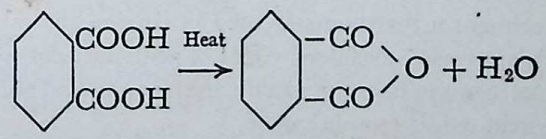
This is a penta-digalloyl-glucose. It is supposed that each hydroxyl group of glucose is esterified by **digallic acid.** A meta digallic acid has been synthesized which has the formula:



It will be noted that one hydroxyl group (in the meta position) of one molecule has formed an ester with the carboxyl group of the other molecule. A synthetic product obtained from glucose and the acid chloride of *m*-digallic acid resembles natural gallotannin in taste, solubility, optical activity, and the precipitation reactions. It is not identical with the natural material, however. Possibly the gallotannin itself contains para-digallic acid groups.

PHTHALIC ACID AND PHTHALIC ANHYDRIDE

The three isomeric dibasic acids, $C_6H_4(COOH)_2$, derived from benzene are phthalic acid (1,2), isophthalic acid (1,3), and terephthalic acid (1,4). All are colorless crystalline solids. **Phthalic acid** is the only one of importance. It is almost insoluble in water; it melts at 191°. On heating just above its melting point, phthalic acid loses a molecule of water and forms **phthalic anhydride,** a cyclic anhydride.



Like succinic anhydride (p. 226), this substance has a five-membered ring.

The meta compound, isophthalic acid, will not form a cyclic anhydride although such an anhydride would contain a six-membered ring as does glutaric anhydride

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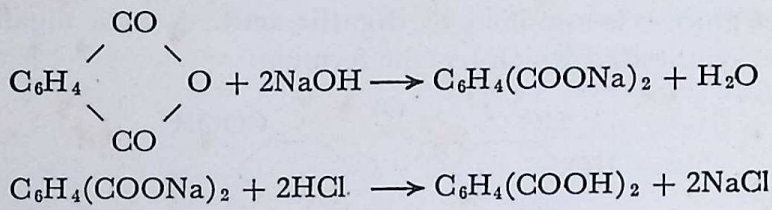
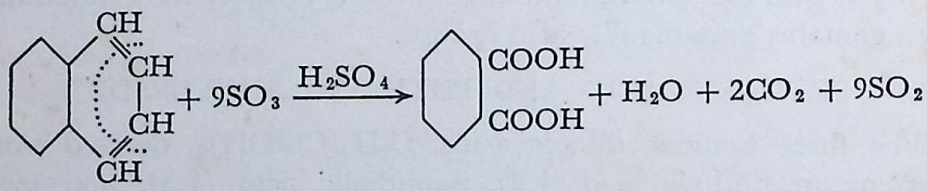
(p. 226). The reason for this failure is evident if one constructs a model of isophthalic acid in which all six atoms of the nucleus are in a plane. It will be seen that the two carboxyl groups in the meta position cannot come near enough together in space to allow the elimination of water. The chain-flexibility in glutaric acid permits the formation of the cyclic anhydride with six atoms in the ring; the rigidity of the planar benzene ring prevents the formation of a similar anhydride from isophthalic acid.

Phthalic anhydride melts at 131° and boils at 285°. It readily sublimes and is purified in this way. On treating with sodium hydroxide solution, the disodium salt of phthalic acid is formed, and on acidifying this solution phthalic acid precipitates.



$$C_6H_4(COONa)_2 + 2HCl \longrightarrow C_6H_4(COOH)_2 + 2NaCl$$

Preparation of Phthalic Anhydride. Phthalic anhydride is of great importance as an intermediate in the dye and resin industries. During 1944 over 122,000,000 lb were produced in this country. It is prepared by oxidizing naphthalene, $C_{10}H_8$. For many years this was done by using fuming sulfuric acid as an oxidizing agent and mercury sulfate as a catalyst.



The enormous amount of sulfur dioxide evolved in the process was piped to a contact sulfuric acid plant. Here it was reoxidized to sulfur trioxide, and used again to make more fuming sulfuric acid.

The discovery that mercury sulfate is an essential factor in the oxidation was the result of an accident. The action of fuming sulfuric acid on naphthalene was being studied; in one experiment a thermometer used in stirring the mixture was broken. Much to the chemist's surprise, excellent yields of phthalic acid were obtained. The action of mercury salts seems to be quite specific in this case, and only in their presence will fuming sulfuric acid oxidize naphthalene.

Since 1918 there has been developed a process for oxidizing naphthalene with air at about 250°. A mixture of the oxides of certain rare metals is the catalyst. If the conditions are not carefully controlled, either complete combustion takes place or the naphthalene comes

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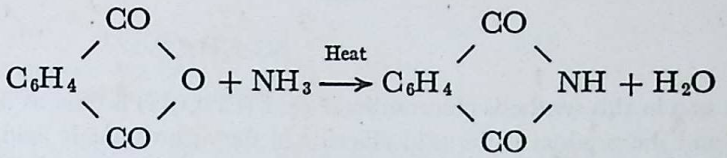
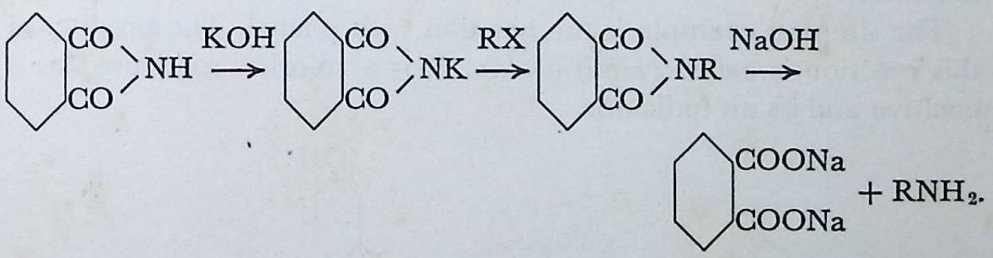
through unchanged. This catalytic process has very largely replaced the older sulfuric acid oxidation. Since phthalic acid very easily loses water, the actual product of the oxidation of naphthalene is not the acid but the anhydride.

Phthalimide. A cyclic imide is formed by the action of ammonia on warm phthalic anhydride.



It will be recalled that amides with two acyl groups attached to the same nitrogen atom are known as *imides* (p. 229). Phthalimide is a crystalline solid which melts at 238°. Like the other amides and imides it has no basic properties, but it has weak acidic properties and forms a salt with potassium hydroxide.

Gabriel's Synthesis of Amines. The potassium salt of phthalimide is used in the preparation of primary amines by Gabriel's synthesis. The potassium atom is replaced by an alkyl group when potassium phthalimide is heated with an alkyl halide. The substituted phthalimide may then be hydrolyzed to the sodium salt of phthalic acid and a primary amine. The equations for the reactions are:



The advantage of this method of preparing primary amines is that the product is free from any secondary or tertiary amines.

Saccharin. An artificial sweetening agent 750 times as sweet as sugar is known as saccharin. Its sweet taste was discovered quite by accident in the course of purely scientific investigation. It is now manufactured for use as a sugar substitute for persons who are suffering from diabetes and cannot eat carbohydrates. It is used in very dilute solution in which the sweet taste is most evident; in moderately concentrated solutions it has a bitter taste. Unlike a real sugar, saccharin is not digested and has no food value: it is thus a sugar substitute only as far as its sweetening power is concerned. Saccharin is the **cyclic imide of ortho sulfobenzoic acid.** It is in no way connected with the sugars. The reason for its sweet taste is a mystery. It is synthesized from toluene by the following steps:

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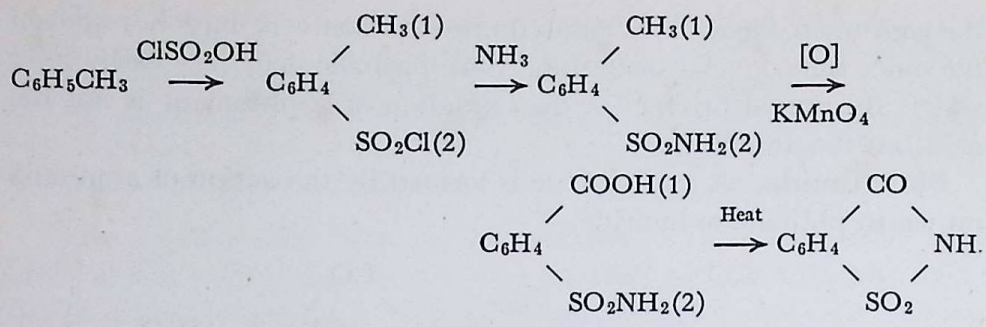
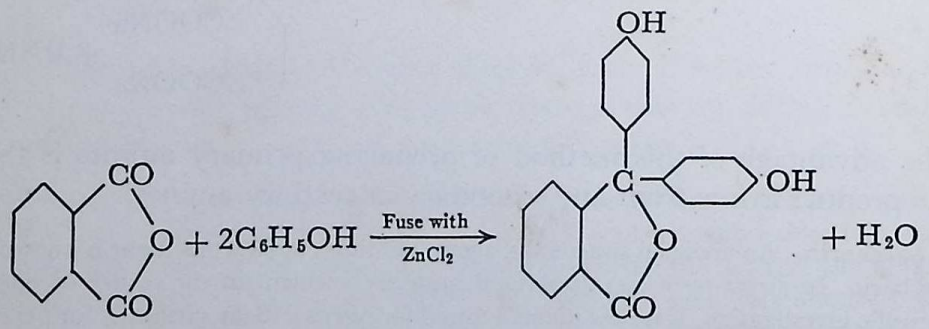


In the first step in this synthesis chlorosulfonic acid ($ClSO_3H$) is used as the sulfonating agent, and the product is the acid chloride of the ortho sulfonic acid, instead of the sulfonic acid itself which is formed if sulfuric acid is used. The hydrogen of the >NH group in saccharin can be replaced by sodium if the compound is treated with sodium hydroxide. This sodium salt is much more soluble than the imide itself, and it is usually in this form that the substance is employed as a sugar substitute.

THE PHTHALEINS

Phenolphthalein. The carbonyl group in phthalic anhydride will react with aromatic compounds containing a reactive ortho or para hydrogen atom. The reaction takes place when the anhydride, the aromatic compound, and a catalyst are heated together. Water is eliminated and a **phthalein** is formed. The phthaleins are dyes and indicators.

The simplest example is the reaction with phenol. The product of this reaction is called *phenolphthalein.* It is a colorless solid used as a laxative and as an indicator.



Phenolphthalein

Phenolphthalein is a lactone of a gamma hydroxy acid. It will be recalled that certain hydroxy acids form lactones rapidly and that the reaction goes to completion; the free acids are unknown and only the sodium salts can be isolated. The free acid of which phenolphthalein is the lactone is also unknown.

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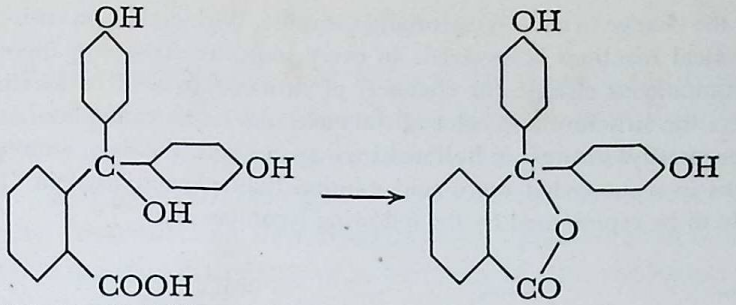
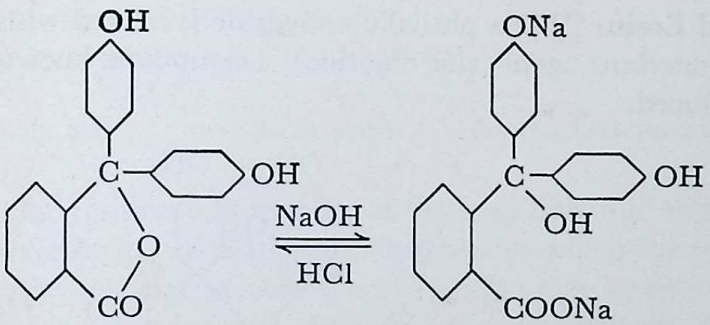


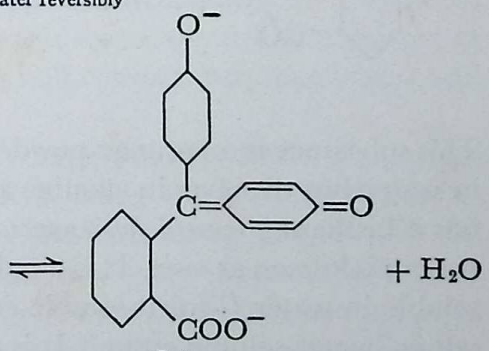
Unknown acid of which phenolphthalein is the lactone

When the lactone ring in phenolphthalein is opened by alkali, the resulting salt loses a molecule of water forming a quinone-like structure in one ring; in addition the other phenolic group forms a salt. The resulting ion, which is stabilized by resonance, is highly colored.



Colorless

Unstable, colorless, loses water reversibly



Red

These changes are practically instantaneous, and they are reversed when the solution is acidified. Consequently phenolphthalein is red in alkaline solution, colorless in acid solution, and can be used as an indicator in the titration of acids and bases.

Other Indicators. There are a great many organic compounds which are used as indicators. Some of them are similar to phenolphthalein in structure, and the

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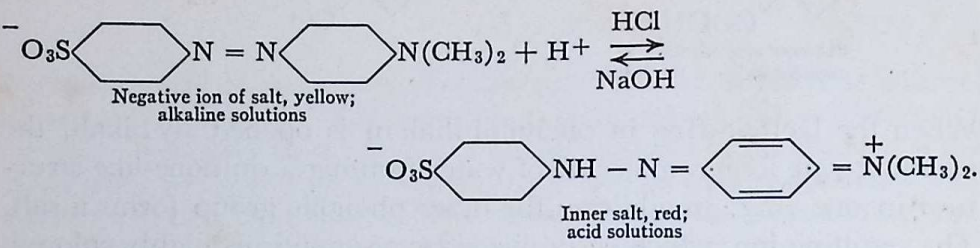
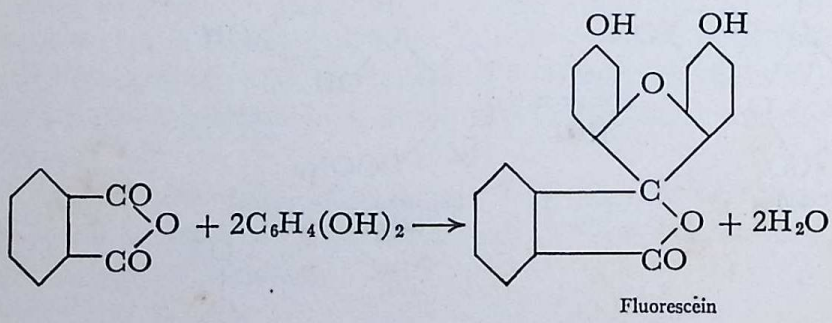
reason for the change in color is essentially the same. With others, an entirely different set of chemical reactions is involved. In every indicator, however, there is a practically instantaneous change (or changes) of structure in acid or alkaline solution which alters the structure and color of the molecule. As an example of another type of indicator, **methyl orange,** or **helianthin,** may be cited. This is a common indicator which turns in a somewhat more acid solution than phenolphthalein. The change is probably to be represented by the following formulas:



Fluorescein and Eosin. When phthalic anhydride is heated with resorcinol and a condensing agent (zinc chloride), a compound known as *fluorescein* is produced.



This substance is an orange powder which is only very slightly soluble in water but dissolves in alkaline solution (as a salt). A dilute solution has a brilliant *green-red fluorescence.* The tetrabromo derivative of fluorescein is known as *eosin.* It is a red powder, soluble in alcohol, and insoluble in water ("spirit-soluble eosin"). Its disodium or ammonium salt is "water-soluble eosin." It is used as a direct dye for silk and as a biological staining material. **Red ink** is usually a dilute solution of water-soluble eosin.

Mercurochrome is a mercury derivative of dibromofluorescein. The group HgOH has replaced one of the hydrogen atoms attached to an aromatic ring. The introduction of a mercury atom is often spoken of as *mercuration;* it conveys strong antiseptic properties to the molecule. Mercurochrome is a bright red, water-soluble solid which is used in dilute solution as an antiseptic.

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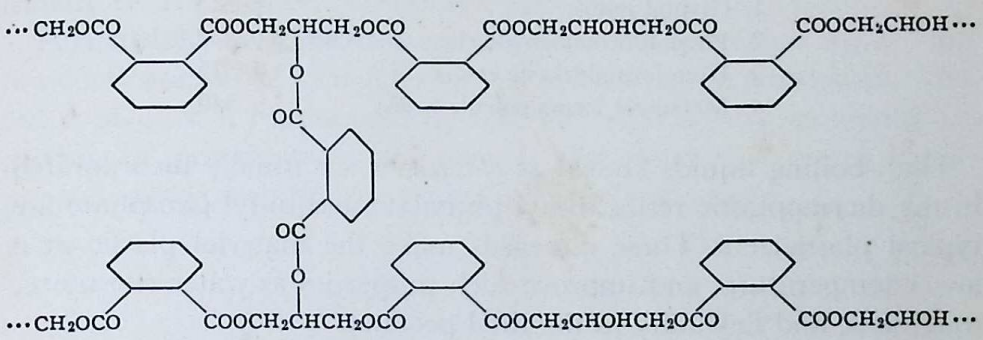
PLASTICS

Alkyd Resins. Phthalic acid is used in large quantities in the preparation of synthetic resins known as *alkyd* or *glyptal resins*. These are materials formed by heating the acid with glycerol. They are similar to the high-molecular-weight esters referred to earlier (p. 229), but, because glycerol has *three* hydroxyl groups, the long chains are *cross linked*. Thus the structure of a portion of the molecule may be represented in the following way.



The position and number of the cross links and the average molecular weight vary with the conditions under which the resin is prepared.

Maleic acid or abietic acid (p. 596) may be substituted for phthalic acid; the resins thus obtained are very similar to those from phthalic acid. They are used principally for protective coatings. In 1944 some 293,000,000 lb of resin was used in this way. About half consisted of phthalic acid alkyds, the remaining half consisted of maleic acid and abietic acid alkyds.

Classification of Plastics. A very large industry based on plastics has developed in the last twenty-five years, the output of plastics materials in the United States in 1944 reaching 784,000,000 lb. Under this heading of plastics one finds a variety of synthetic organic compounds of high molecular weight, all of which have the property of being plastic at temperatures somewhat above the boiling point of water (125° to 200°). This enables a great variety of articles to be manufactured by pressing the hot plastic into molds (pressures of 4 tons per square inch are commonly used); then cooling and extruding the product. Some plastics soften on reheating; they are known as *thermoplastics*. Others when once set are no longer fusible; they are known as *thermosetting* resins. The following table lists some of the common materials of each type.

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CLASSIFICATION OF PLASTICS

A. Thermoplastics	
1. Cellulose acetate	p. 299
2. Ethenoid plastics	
Polythene	p. 63
Polystyrene	p. 530
Polyvinyl compounds	p. 305
Polyacrylic esters	p. 309
Polymethylacrylic esters	p. 310
B. Thermosetting Plastics	
1. Glyptal resins	p. 513
2. Phenol formaldehyde resins (Bakelite)	p. 432
3. Urea formaldehyde resins	p. 515
4. Melamine formaldehyde resins	p. 340

High-boiling liquids known as *plasticizers* are usually incorporated in the thermoplastic resins. Butyl phthalate and butyl phosphate are typical plasticizers. These materials make the material plastic at a lower temperature, and improve such properties as water resistance, toughness, and flexibility in the final product.

The difference between thermoplastic and thermosetting plastics in chemical terms is essentially the following: the molding operation does not change the molecular weight or chemical structure of the thermoplastic materials, but it does change the molecular weight and chemical structure of the thermosetting resins. At the molding temperature a further chemical reaction takes place, the average molecular weight of the material increases, and additional cross links form between the long chains. In the glyptal resins the chemical reaction is esterification; in the formaldehyde resins it is condensation. In both, cross linking is very important since it is the cross links in material of high molecular weight which makes it soften less on heating and dissolve or swell less on treatment with a solvent. The student will recall that in the vulcanization of rubber the cross linking between molecules brings about great changes in physical properties. The process of vulcanization is very similar to the thermosetting of a plastic.

The final products of heating thermosetting plastics are hard, tough, very insoluble materials. It is interesting to compare such materials with the tough insoluble fibers of both natural and synthetic origin (cotton, silk, Nylon). In the fibers, a favorable arrangement of long-chain molecules with strong intermolecular forces binds many molecules together in a crystal-like pattern. The intermolecular

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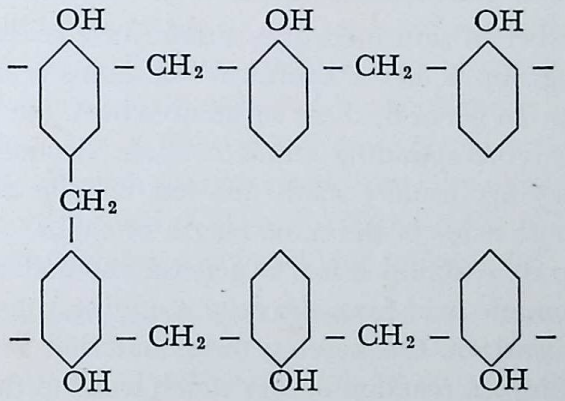
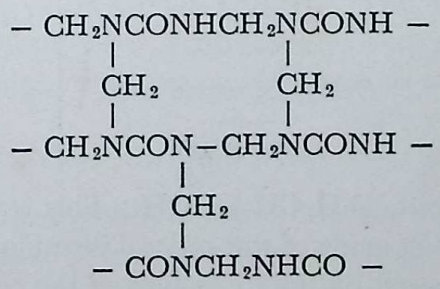
forces in such high molecular weight materials largely determine their toughness and insolubility. In the thermosetting resins, by contrast, direct covalent links hold together chains of long molecules. The results are similar as far as toughness and insolubility are concerned, but the special properties of fibers are lacking in the thermosetting materials. In the thermoplastic resins, the amorphous material is composed of smaller molecules than in the thermosetting plastics, and, because there is only random orientation, the intermolecular forces are relatively weak. Hence the materials are *thermoplastic* and usually swell or dissolve in suitable solvents.

Formaldehyde Resins. A group of related plastics is formed by the condensation of formaldehyde with a variety of substances. The oldest of these is represented by Bakelite (p. 432), the condensation product of formaldehyde and phenol. The characteristic link in the phenolic resins may be represented in the following way.



As in the glyptal resins, long chains tied together by cross links give a very hard insoluble material as the final product. In the formaldehyde-urea resins the long chains are tied together with many methylene cross links.



Melamine can condense with formaldehyde in a fashion similar to that shown for urea.

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The first condensation products of the formaldehyde type resins are of relatively low molecular weight and are prepared by heating the components for a short time with small amounts of alkali or ammonia as a catalyst. The result with the phenolic resins is an amorphous material which is insoluble in water but soluble in many organic solvents. Various fillers, such as wood pulp, are mixed with the powdered material, coloring matter is added, and the mixture is heated in molds under pressure. The resin then sets to the final product.

The first condensation products of the urea-formaldehyde and the melamine-formaldehyde type are water soluble. This enables one to apply them to various materials including textiles. On heating, the condensation proceeds further and water-insoluble products are formed.

ACIDS WITH CARBOXYL GROUP IN THE SIDE CHAIN

A great number of saturated and unsaturated acids are known in which an aryl group is one or more carbon atoms removed from the carboxyl group. In general, these substances have the same chemical reactions as the corresponding aliphatic acids. Because of the heavy aryl group, they are usually solids and less volatile and less soluble than the aliphatic acids of the same length of chain.

The Willgerodt reaction offers a general method of synthesizing this type of aromatic acid from the corresponding ketone, alcohol, or ethylenic hydrocarbon. On heating these materials with ammonium polysulfide a complex reaction occurs which leads to the formation of the acid amide.

$$\left.\begin{array}{ll} C_6H_5CH = CH_2 & \xrightarrow[\text{above } 200^\circ]{(NH_4)_2S_x \text{ sealed tube}} \\ C_6H_5CHOHCH_3 & \xrightarrow[\text{above } 200^\circ]{(NH_4)_2S_x \text{ sealed tube}} \\ C_6H_5COCH_3 & \xrightarrow[\text{above } 200^\circ]{(NH_4)_2S_x \text{ sealed tube}} \end{array}\right\} C_6H_5CH_2CONH_2$$

Phenylacetic Acid, $C_6H_5CH_2COOH$. This is the simplest representative of a series of acids of the general formula $Ar(CH_2)_nCOOH$. It can be best prepared by the hydrolysis of the corresponding nitrile which is readily formed from benzyl chloride (p. 420) and sodium cyanide.

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$$\underset{\text{Benzyl chloride}}{C_6H_5CH_2Cl} + NaCN \longrightarrow \underset{\text{Benzyl cyanide}}{C_6H_5CH_2CN} + NaCl$$

$$C_6H_5CH_2CN + 2H_2O \xrightarrow[\text{catalyst}]{\text{Acid}} C_6H_5CH_2COONH_4$$

$$C_6H_5CH_2COONH_4 + HCl \longrightarrow C_6H_5CH_2COOH + NH_4Cl$$

Phenylacetic acid melts at 76° and boils at 265°. It is only very sparingly soluble in water. It is used in small quantities in the form of its ethyl ester in the perfume industry.

Cinnamic Acid and Hydrocinnamic Acid. The unsaturated acid, cinnamic acid, $C_6H_5CH = CHCOOH$, is readily prepared from benzaldehyde by the Perkin reaction as described in the last chapter. It occurs in certain essential oils and plant gums. Four modifications of cinnamic acid are known; they are all crystalline solids with different melting points. The common form of the acid melts at 133°; it is believed to be the *trans* form. The other modifications are different crystallographic forms of the *cis* acid; the difference in melting point is probably due to a different arrangement of the molecules in the crystal as in the two modifications of benzophenone (p. 492).

Cinnamic acid has all the typical reactions of an α,β-unsaturated acid. On reduction with sodium amalgam or by catalytic hydrogenation, hydrocinnamic acid, $C_6H_5CH_2CH_2COOH$, is formed. This is also known as β-phenylpropionic acid. It melts at 48°.

Phenylpropiolic Acid, $C_6H_5C \equiv CCOOH$. The ester of cinnamic acid readily adds a molecule of bromine forming a dibromide. On boiling this with alcoholic potassium hydroxide, an acid with an acetylenic linkage is formed.

$$\underset{\text{Ethyl cinnamate}}{C_6H_5CH = CHCOOC_2H_5} + Br_2 \longrightarrow C_6H_5CHBrCHBrCOOC_2H_5$$

$$C_6H_5CHBrCHBrCOOC_2H_5 + 3KOH \longrightarrow C_6H_5C \equiv CCOOK + 2KBr + C_2H_5OH + 2H_2O$$

Mandelic Acid, $C_6H_5CHOHCOOH$. The addition of hydrocyanic acid to benzaldehyde yields an hydroxy nitrile. This on hydrolysis forms an alpha hydroxy acid known as *mandelic acid*.

$$C_6H_5CHO + HCN \longrightarrow C_6H_5CHOHCN \xrightarrow{\text{Hyd.}} C_6H_5CHOHCOOH$$

The hydroxy nitrile corresponding to mandelic acid occurs as the glucoside, amygdalin, present in bitter almonds (p. 482). Its enzymatic hydrolysis to benzaldehyde, hydrocyanic acid, and sugar has already been referred to.

Mandelic acid is a crystalline solid which melts at 118°. Its re-

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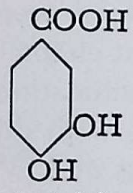
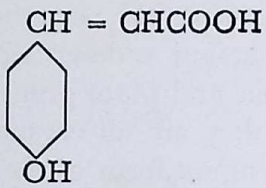
actions are those typical of an alpha hydroxy acid (Chap. 12). Its ammonium salt has found use in medicine as a urinary antiseptic.

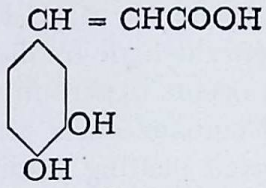
Occurrence of Aromatic Acids in Plants. The following aromatic acids have been found widely distributed in the plant kingdom: benzoic acid, salicylic acid (usually as the methyl ester), gallic acid, protocatechuic acid (and ester), *p*-hydroxycinnamic acid (cumaric acid) and 3,4-dihydroxycinnamic acid (caffeic acid). The formulas for the acids in this list which have not been previously considered are given below.



Protocatechuic acid



p-Hydroxycinnamic acid or *p*-cumaric acid



3,4-Dihydroxycinnamic acid or caffeic acid

In addition to these six substances but few other aromatic acids have been isolated from the plant world, and none found so widely distributed. The close relationship of these acids to each other is evident.

Mellitic acid, $C_6(COOH)_6$, occurs as an aluminum salt called *honeystone* in lignite and peat beds. It can be prepared by the oxidation of graphite or charcoal with nitric acid. Although mellitic acid contains six carboxyl groups it is difficult to esterify by the ordinary method using alcohol and a small amount of a mineral acid as a catalyst: each carboxyl group has two other carboxyl groups substituted in the ortho positions (cf. p. 502).

Depsides. A number of compounds are found in plants in which two molecules of hydroxy acids are united through an ester linkage. For example, digallic acid is such a compound. The name *depside* has been given to this class of substances. Di-depsides contain two such molecules thus joined, tri-depsides three, etc. Gallotannin is thus a complex di-depside, and probably other tannins contain the depside linkage.

A few simple di-depsides have been isolated from plants. One of these, derived from **orsellinic acid,** $C_6H_2(COOH)(OH)_2CH_3$ (1,2,3,5), has been isolated from lichens. This hydroxy acid, which contains a methyl group, seems to be a characteristic constituent of lichens, and is not found in other classes of plants.

QUESTIONS AND PROBLEMS

1. Compare the chemical behavior of benzoyl chloride and *n*-valeryl chloride.

2. Write equations showing how to prepare benzoic acid from aniline, acetophenone, phthalic acid, benzenesulfonic acid, bromobenzene, and *p*-toluidine.

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3. How many products would you expect to obtain by the addition of bromine to cinnamic acid? Would they be optically active? Would they be resolvable?

4. Write structural formulas for benzotrichloride, hydrocinnamic acid, phenylpropiolic acid, fluorescein.

5. What is an indicator? Using phenolphthalein as an example, explain in chemical terms the color changes that take place going from acid to alkaline solution and back.

6. Describe two commercial methods of preparing phthalic anhydride. What are some important industrial uses of this material?

7. Write equations for the preparation of salicylic acid from coal tar, and for the preparation of three important medicinals from salicylic acid.

8. Define and illustrate the following terms: *steric hindrance*, *plasticizer*, *thermosetting plastic*, *depside*, *thermoplastic resin*.

9. Show how the Willgerodt reaction can be used to synthesize aromatic acids with the carboxyl groups in a side chain.

10. Outline the steps in the Gabriel synthesis of primary amines. Give equations for three other general methods of preparing primary amines.

11. Explain the chemical reactions involved in the formation of alkyd resins. When are these resins thermosetting and when thermoplastic?

12. Predict the behavior of the following acids when heated in ethyl alcohol containing a small amount of sulfuric acid: $(CH_3)_3CCH_2CH_2COOH$; 2,6-diiodobenzoic acid; $CH_3CH_2C(CH_3)_2COOH$; $C_6H_3(COOH)_3$-1,2,3, mellitic acid.

13. Outline a chemical method for separating a mixture of benzaldehyde, butyric acid, salicylaldehyde, and ethyl benzoate.

14. Discuss briefly the preparation, structure, and uses of the formaldehyde plastics.

15. The compound $C_8H_6O_2Cl_2$ dissolves in sodium bicarbonate solution and can be recovered on acidification. It can be boiled with alcoholic alkali without change. When oxidized vigorously it yields a dibasic acid. The dibasic acid loses water on heating and readily forms a neutral ester on boiling with alcohol and a little sulfuric acid. What is the structural formula of the compound $C_8H_6O_2Cl_2$?

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Chapter 27

AROMATIC CARBINOLS AND ARYL DERIVATIVES OF ALIPHATIC HYDROCARBONS: TRIPHENYLMETHANE DYES

AROMATIC CARBINOLS

The simplest aromatic carbinol is the phenyl derivative of methyl alcohol, $C_6H_5CH_2OH$. This is known as *benzyl alcohol*. The homologs of this substance in which the phenyl group is one or more carbon atoms removed from the functional group are so like the aliphatic compounds that we shall not consider them. On the other hand, the secondary and tertiary carbinols in which the aryl groups are directly connected to the $-\overset{\diagdown}{\underset{\diagup}{C}}OH$ group, have certain peculiar and interesting reactions which are worthy of discussion. When the hydroxyl group itself is directly attached to an aryl group, we have a phenol. The distinction between phenols and aromatic carbinols is profound. These two classes of compounds have little in common: the aromatic carbinols are similar to the aliphatic carbinols; the phenols are like the aliphatic enols.

Benzyl Alcohol, $C_6H_5CH_2OH$. In all its reactions this compound is a typical primary alcohol. The physical properties, however, are different from the simple aliphatic alcohols. It is a colorless liquid which boils at 206°, possesses a faint, pleasant odor, and is only very slightly soluble in water.

Benzyl alcohol occurs in a variety of plants, usually as an ester. It is prepared for use in the perfume industry either from benzaldehyde by the Cannizzaro reaction (p. 483) or by the hydrolysis of benzyl chloride (p. 420).

$$C_6H_5CH_2Cl + H_2O \xrightarrow[Na_2CO_3]{\text{Heated}} C_6H_5CH_2OH + HCl \text{ (neutralized by } Na_2CO_3\text{)}$$

One of the differences between benzyl alcohol and the aliphatic primary alcohols is that it reacts with concentrated hydrochloric acid

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at *room temperature* to form benzyl chloride. The rates of reactions involving the hydroxyl group are somewhat increased by the presence of the phenyl group. The other reactions of benzyl alcohol are those which are characteristic of a primary alcohol. For example, it can be oxidized to benzaldehyde and eventually to benzoic acid.

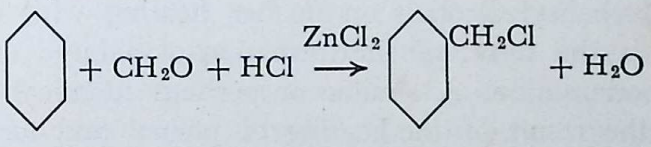
$$C_6H_5CH_2OH \xrightarrow{[O]} C_6H_5CHO \xrightarrow{[O]} C_6H_5COOH$$

It is readily esterified by heating with an organic acid and a mineral acid as a catalyst. Benzyl acetate, $CH_3COOCH_2C_6H_5$, can be thus prepared. It is also formed by heating benzyl chloride with potassium acetate. It is a pleasant-smelling liquid used in the perfume industry.

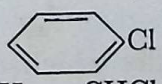
$$CH_3COOK + ClCH_2C_6H_5 \longrightarrow CH_3COOCH_2C_6H_5 + KCl$$

Benzyl Chloride. Benzyl chloride, $C_6H_5CH_2Cl$, is always manufactured by the chlorination of boiling toluene (p. 420). Benzyl chloride is a liquid which boils at 178°; it has a pungent odor and a powerful effect on the tear glands (lachrymatory action).

Benzyl chloride can also be prepared from benzene, formaldehyde, and hydrogen chloride in the presence of a condensing agent such as zinc chloride. The reaction, known as *chloromethylation*, is also applicable to the alkylbenzenes.

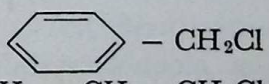


The halogen atom in benzyl chloride is reactive, and the typical reactions of alkyl halides are also characteristic of this substance. For example, potassium cyanide reacts with benzyl chloride, forming **benzyl cyanide,** $C_6H_5CH_2CN$ (p. 517), from which phenylacetic acid is prepared. Such metathetical reactions proceed more rapidly with benzyl chloride than with the simple alkyl halides. It will be recalled that this was also true of allyl chloride ($CH_2 = CHCH_2Cl$), while vinyl chloride ($CH_2 = CHCl$) was very unreactive (Chap. 16). The phenyl group is thus similar to a vinyl group in its action; C_6H_5Cl is very unreactive, while $C_6H_5CH_2Cl$ is somewhat more reactive than an alkyl halide.



$CH_2 = CHCl$

Very unreactive



$CH_2 = CH - CH_2Cl$

Somewhat more reactive than $CH_3CH_2CH_2Cl$

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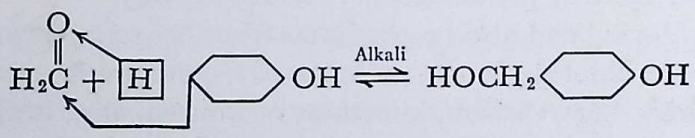
Hydroxybenzyl Alcohols. Ortho hydroxybenzyl alcohol, $HOC_6H_4CH_2OH$ (1,2), is known as *saligenin.* It occurs as the glucoside, **salicin,** in the bark of various species of trees. The wide distribution in the plant world of the oxidation products of saligenin will be recalled. These are salicylic aldehyde (and its condensation product, coumarin) and salicylic acid. The chemical changes which occur in growing plants certainly include oxidation and reduction reactions; very probably all these ortho hydroxyl compounds have a common biochemical origin.

A mixture of ortho hydroxybenzyl alcohol and para hydroxybenzyl alcohol, $HOC_6H_4CH_2OH$ (1,4), is formed by the condensation of phenol and formaldehyde in the presence of alkali. This reaction is very similar to an aldol condensation (p. 137); the hydrogen in the ortho or para position is the equivalent here of the alpha hydrogen atom of a ketone or aldehyde. Like the aldol condensation, the reaction appears to be reversible.



Both hydroxybenzyl alcohols on further heating with alkali form resins; this is the result of the formation of a large molecule by repeated condensation. A similar or perhaps identical product is formed as the result of the heating of phenol and formaldehyde (p. 515).

Cinnamic Alcohol, $C_6H_5CH = CHCH_2OH$. This unsaturated alcohol is found in plants combined with cinnamic acid. The ester of cinnamic alcohol and cinnamic acid is the principal constituent of many balsams, of which the commonest is **storax.** The occurrence in plants of cinnamic alcohol, cinnamic aldehyde, and cinnamic acid points to a ready biochemical interconversion of these compounds comparable to that suggested above for the oxidation products of saligenin. The wide distribution of benzaldehyde (usually as a complex glucoside) is also of significance as the cinnamic compounds are transformed into this aldehyde by oxidation or formed from it by condensation (p. 485).

Cinnamic alcohol crystallizes in white needles which melt at 35° to a liquid which boils at 257°. It has the odor of hyacinth, and is used in the perfume industry. It may be prepared synthetically by the

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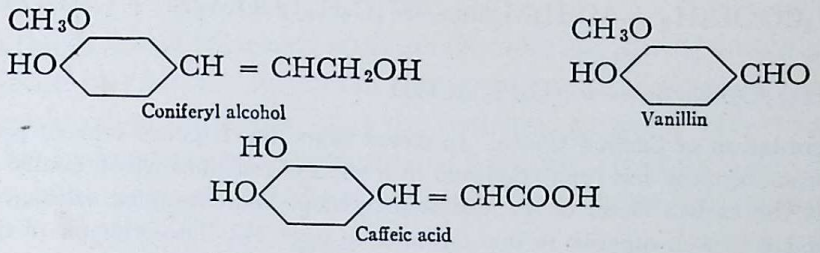
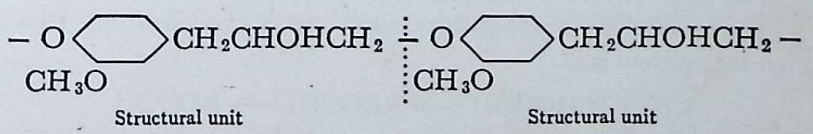
cautious reduction of cinnamic aldehyde (certain reducing agents, in particular aluminum isopropoxide, p. 134, will reduce the aldehyde group to CH_2OH without attacking the ethylenic linkage). Cinnamic alcohol may be regarded as a phenyl derivative of allyl alcohol (p. 306). Its chemical properties are very similar to those of the parent compound and need not be enumerated.

Coniferyl alcohol occurs as the glucoside, **coniferin,** in the sap of coniferous trees. It is related to vanillin just as cinnamic alcohol is related to benzaldehyde.



Caffeic acid (p. 518) is the corresponding acid but with the two phenolic groups free.

Lignin. It will be recalled that the cellulose aggregates in wood fiber are associated with an amorphous material of high molecular weight known as *lignin* (p. 295). Investigations of this amorphous material indicate that it is probably related to coniferyl alcohol and caffeic acid. Like other natural products of high molecular weight, there seems to be a regular recurrence of a definite structural unit. The probable fundamental unit of lignin is indicated in the following formula which has been tentatively suggested.



The units are joined by the ether linkage from one primary hydroxyl group to the phenolic group of the next molecule. Coniferyl alcohol could be formed from a molecule of the simple unit by dehydration; caffeic acid would result from oxidation and demethylation.

Synthesis of Secondary and Tertiary Carbinols. Secondary and tertiary alcohols containing aryl groups may be prepared by the same reactions employed in the aliphatic series. For example, benzophenone on reduction yields the secondary alcohol, **diphenylcarbinol,** $C_6H_5CHOHC_6H_5$ (mp 68°). The same ketone on treating with phenylmagnesium bromide forms **triphenylcarbinol,**

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$$C_6H_5COC_6H_5 \xrightarrow{[H]} \underset{\text{Diphenylcarbinol}}{C_6H_5CHOHC_6H_5}$$

$$C_6H_5COC_6H_5 + C_6H_5MgBr \longrightarrow (C_6H_5)_3COMgBr$$

$$(C_6H_5)_3COMgBr \xrightarrow{H_2O} \underset{\text{Triphenylcarbinol}}{(C_6H_5)_3COH}$$

Another obvious method of preparing triphenylcarbinol is by the action of phenylmagnesium bromide on ethyl benzoate.

$$C_6H_5COOC_2H_5 + 2C_6H_5MgBr \longrightarrow (C_6H_5)_3COMgBr + C_2H_5OMgBr$$

$$(C_6H_5)_3COMgBr \xrightarrow{H_2O} (C_6H_5)_3COH$$

Degradation of Carbon Chain. In recent years the Grignard reagent prepared from bromobenzene has been employed in a series of reactions which enable one to degrade the carbon chain of an acid step by step. With complex substances this method has proved superior to that outlined on page 242. The principle of the two methods is not dissimilar. The ester of the acid in question is converted to a carbinol by the reaction given above. The carbinol on oxidation is cleaved to benzophenone and an acid with one less carbon than the original acid.

$$RCH_2COOH \longrightarrow \text{ester} \xrightarrow{C_6H_5MgBr} RCH_2C(OH)(C_6H_5)_2 \xrightarrow{CrO_3} RCOOH$$

If a branched chain is present in the position next to the carbonyl group, a ketone is formed as the first oxidation product. However, with the strong oxidizing agent employed (CrO_3), the ketone is usually not isolated but is oxidized with further cleavage to an acid. Thus, if a methyl group is located on the carbon atom adjacent to the carboxyl group, the result of this degradation is an acid with *two* less carbon atoms than the original acid.

$$R(CH_3)CHCOOH \longrightarrow RCOCH_3 \longrightarrow RCOOH$$

Triphenylcarbinol. This compound is a colorless solid which melts at 163°. It is the simplest representative of a large class of compounds of the general formula Ar_3COH. Many such compounds have been synthesized because of their interesting and somewhat unusual chemical properties and their relation to the triphenylmethane dyes.

As would be expected from the fact that it is a tertiary alcohol, triphenylcarbinol is not oxidized. Since there is no hydrogen atom on a carbon atom adjacent to the functional group, it can not lose water and form an unsaturated hydrocarbon as most aliphatic alcohols so readily do.

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It will be remembered that tertiary butyl alcohol as a typical tertiary alcohol reacts very rapidly with hydrochloric acid; so does triphenylcarbinol. The hydroxyl group is perhaps even more readily replaced than in the aliphatic tertiary alcohols, since the influence of the phenyl group (noted even in benzyl alcohol) is in this direction. When dry hydrogen chloride is passed into a solution of the carbinol, the corresponding chloride forms almost at once.

$$(C_6H_5)_3COH + HCl \xrightarrow[\text{rapidly}]{\text{Very}} (C_6H_5)_3CCl + H_2O$$

When the carbinol is treated with acetyl chloride, the hydroxyl group is replaced by chlorine instead of the acetate being formed. This may be considered as indicating that the hydroxyl group is very reactive, and the hydrogen very *un*reactive. The same reaction takes place with the few tertiary, aliphatic carbinols which have been studied.

$$(C_6H_5)_3C \boxed{OH + CH_3CO} Cl \longrightarrow (C_6H_5)_3CCl + CH_3COOH$$

Another characteristic reaction of triphenylcarbinol is that with formic acid; the carbinol is reduced to the hydrocarbon, triphenylmethane.

$$(C_6H_5)_3COH + HCOOH \longrightarrow (C_6H_5)_3CH + H_2O + CO_2$$

Triphenylchloromethane, $(C_6H_5)_3CCl$. This chloride may be readily prepared from the corresponding carbinol as we have seen. It can also be conveniently synthesized by the Friedel-Crafts reaction from benzene and carbon tetrachloride; the temperature of the reaction mixture is kept higher than when the dichloride is made from the same reactants (p. 492).

$$3C_6H_6 + CCl_4 \xrightarrow{AlCl_3} (C_6H_5)_3CCl + 3HCl$$

Triphenylchloromethane is a colorless solid which melts at 112°. The chlorine atom is replaced with extraordinary ease by a hydroxyl or methoxyl group when the chloride is allowed to react with water or alcohol.

$$(C_6H_5)_3CCl + H_2O \xrightarrow[\text{rapidly}]{\text{Very}} (C_6H_5)_3COH$$

The peculiar compound formed by treating triphenylchloromethane with metals will be discussed later in this chapter.

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Basicity of Triarylcarbinols. Triphenylcarbinol and its derivatives dissolve in concentrated mineral acids with the formation of highly colored salts. This phenomenon is known as *halochromism*. Concentrated sulfuric acid is necessary in order to convert triphenylcarbinol completely to the halochromic salt. The para trimethoxy derivative, $(CH_3OC_6H_4)_3COH$, however, forms a halochromic salt even with aqueous hydrochloric acid. These halochromic salts may often be isolated as highly colored crystalline solids; the perchlorates are particularly easily obtained. A study of these compounds has shown that they are salts formed from the carbinol and acid by loss of water. Since the positive charge is probably located on a carbon atom they are often called *carbonium salts*. Like almost all ionic reactions, their formation or hydrolysis is practically instantaneous.

$$(C_6H_5)_3COH + HX \rightleftharpoons \underset{\text{Highly colored}}{(C_6H_5)_3C^+} + X^- + H_2O$$

It should be noted that the colorless triphenylchloromethane is *not* a halochromic salt. On dissolving in some solvents, however, it probably dissociates at least in part, forming the colored ion, $(C_6H_5)_3C^+$, and the chloride ion.

It is extremely probable that the basicity of triphenylcarbinol is due to the fact that the resulting ion is an ionic hybrid stabilized by a considerable amount of resonance energy. The resonating structures would be those in which the positive charge is located at the ortho or para positions of the aromatic nuclei, which are in the ortho or para quinoid state. Two such structures would be possible for each aryl group. The structure of one may be written as $(C_6H_5)_2C =$. An ion R_3C^+ in which all the groups are *alkyl* would not have the possibility of resonance. It is significant that the trialkyl carbinols do not have basic properties.

ARYL DERIVATIVES OF ALIPHATIC HYDROCARBONS

Aryl Derivatives of Methane. Toluene is the simplest aryl derivative of methane. The phenyl derivatives of methane are listed below, together with their physical properties.

PHYSICAL PROPERTIES OF PHENYL DERIVATIVES OF METHANE

Name	*Formula*	*Melting Point*	*Boiling Point*
Toluene	$C_6H_5CH_3$	− 95°	111°
Diphenylmethane	$(C_6H_5)_2CH_2$	27°	262°
Triphenylmethane	$(C_6H_5)_3CH$	92°	359°
Tetraphenylmethane	$(C_6H_5)_4C$	285°	431°

With the exception of the tetraphenyl compound, they are all relatively easily oxidized. The final products are benzoic acid, benzophenone, and triphenylcarbinol, respectively.

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$$C_6H_5CH_3 \xrightarrow{[O]} C_6H_5CHO \xrightarrow{[O]} C_6H_5COOH$$

$$\begin{matrix} C_6H_5 \\ \diagdown \\ \quad CH_2 \\ \diagup \\ C_6H_5 \end{matrix} \xrightarrow{[O]} (C_6H_5)_2CHOH \xrightarrow{[O]} (C_6H_5)_2CO$$

$$(C_6H_5)_3CH \xrightarrow[\substack{CrO_3 \\ \text{Very rapid}}]{[O]} (C_6H_5)_3COH$$

The ease with which the last two oxidations may be brought about illustrates the influence exerted by the accumulation of phenyl groups on the carbon atom.

Triphenylmethane. This hydrocarbon may be synthesized from benzene and chloroform by the Friedel-Crafts reaction.

$$3C_6H_6 + CHCl_3 \xrightarrow{AlCl_3} (C_6H_5)_3CH + 3HCl$$

It may also be prepared by reducing triphenylchloromethane with zinc and an acid, or from the ethyl ether of triphenylcarbinol by heating with aluminum chloride. In this reaction, the ethoxy group is oxidized to acetaldehyde.

$$(C_6H_5)_3COCH_2CH_3 \xrightarrow{AlCl_3} (C_6H_5)_3CH + CH_3CHO$$

Acidic Properties of Triarylmethanes. The triarylmethanes, Ar_3CH, of which triphenylmethane is an example, have very weak acidic properties. Triphenylmethyl sodium, $(C_6H_5)_3CNa$, may be formed, for example, by the action of metallic sodium in liquid ammonia solution on the hydrocarbon.

$$(C_6H_5)_3CH + Na \longrightarrow (C_6H_5)_3CNa + [H]$$

Such salts of the arylated methanes are highly colored, and soluble in organic solvents. They are undoubtedly somewhat dissociated into the ions $(C_6H_5)_3C^-$ and Na^+. A similar salt of diphenylmethane may be prepared by indirect methods. The diarylmethanes are much weaker acids than even the triarylmethanes, however. The effect of the phenyl group on the methane carbon atom is thus cumulative. Triphenylmethane is a much weaker acid than even an aliphatic alcohol, and sodium triphenylmethyl reacts with alcohol as follows:

$$(C_6H_5)_3CNa + C_2H_5OH \longrightarrow (C_6H_5)_3CH + NaOC_2H_5$$

It is a matter of considerable interest that triphenylmethane has weakly acidic properties and triphenylcarbinol weakly basic properties. The presence of three phenyl groups appears to make possible the formation of either the ion $(C_6H_5)_3C^+$ or $(C_6H_5)_3C^-$. The explanation of the stability of these ions as compared to similar ones containing only alkyl groups is that the presence of aryl groups permits of resonance.

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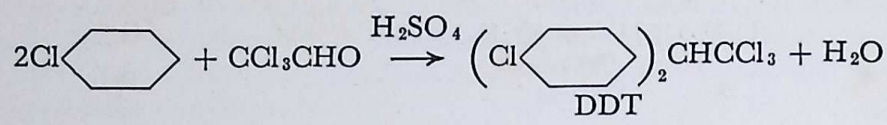
Aryl Derivatives of Ethane. Two aryl derivatives of ethane require our attention; one because of its practical importance, the other for its scientific interest. The first is *p,p'*-dichlorodiphenyl-trichloroethane, more generally known as DDT. It is prepared by the condensation of chlorobenzene with chloral, and it finds extensive use as an insecticide.



The second is hexaphenylethane, $(C_6H_5)_3CC(C_6H_5)_3$, a hydrocarbon in which the accumulation of phenyl groups has led to some remarkable properties.

Hexaphenylethane was first prepared in 1900 by Gomberg.[1] The reaction he employed was similar to a Wurtz reaction.

$$2(C_6H_5)_3CCl + 2Ag \longrightarrow (C_6H_5)_3C - C(C_6H_5)_3 + 2AgCl$$

The resulting compound was a colorless, crystalline solid, as one would expect. But quite contrary to expectations *its solutions were orange*, and more surprising still *they absorbed oxygen* from the air with great rapidity. The oxygen absorption discharged the color of the solution, and a new, colorless, crystalline material separated. This compound on analysis proved to be a **peroxide,** $(C_6H_5)_3C - O - O - C(C_6H_5)_3$.

A careful study of hexaphenylethane and other hexaarylethanes has shown that the behavior of these substances is due to the fact that in solution they are dissociated into *free radicals*. Thus, in a solution of hexaphenylethane there is always a mobile equilibrium between hexaphenylethane itself and **triphenylmethyl,** $(C_6H_5)_3C -$, the so-called free radical.

$$(C_6H_5)_3C - C(C_6H_5)_3 \rightleftharpoons 2(C_6H_5)_3C -$$

This free radical is colored and extraordinarily reactive. It combines with oxygen and halogens and is irreversibly polymerized in the presence of acids. The degree of dissociation increases with dilution according to the law of mass action. The equilibrium is shifted in favor of the free radical by raising the temperature. At 5° the dissociation of hexaphenylethane in a 2 per cent solution is not more than a few per cent. At 80°, however, the dissociation is 20 per cent, as

[1] Moses Gomberg (1866–1947). Professor of chemistry at the University of Michigan.

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shown by the molecular weight determination in freezing naphthalene.

Other Free Radicals. Some hexaarylethanes are practically completely dissociated in solution at room temperature. Probably the crystalline solid even in such molecules, however, is the ethane and not the free radical. In solution, at least, a number of organic compounds exist in a form in which one of the carbon atoms is trivalent. These free radicals are exceptions to the general rule of the tetravalence of carbon, but their existence in no way affects the validity of the structural theory which was largely developed before their existence was discovered. The carbon to carbon linkage in ethane ($CH_3 - CH_3$), butane ($C_2H_5 - C_2H_5$), and biphenyl ($C_6H_5 - C_6H_5$) is very different from that in hexaphenylethane. These simpler compounds do not dissociate into free radicals under ordinary conditions.

The difference between ethane and hexaphenylethane probably is connected both with the peculiar degree of unsaturation of aromatic groups and with the fact that they occupy more space than simple alkyl groups. Neither tetraphenylmethane, tetraphenylethane, nor pentaphenylethane at room temperature shows any of the peculiarities of hexaphenylethane. On the other hand, derivatives of ethane with only four aryl groups and two *branched* alkyl groups have been prepared which, like hexaphenylethane, are dissociated into free radicals.

The action of aromatic groups in promoting the dissociation is well explained by the assumption that the free radical is stabilized by resonance of the radical due to the possibility of the free bond shifting into the aromatic ring. The effect of the branched alkyl groups is probably due to their steric effect in weakening the C — C linkage.

For many years all attempts to prepare free methyl and free ethyl radicals were without success. The products were always the well-known saturated or unsaturated hydrocarbons. However, evidence has been obtained that free methyl and free ethyl groups are formed at high temperatures by the thermal decomposition of hydrocarbons or metalloorganic compounds. Thus the vapor of lead tetramethyl, $Pb(CH_3)_4$, when passed rapidly through a hot tube decomposes with the formation of some **free methyl groups,** CH_3-. These very soon combine to form ethane, however, and their presence can only be detected by special methods. It is evidently quite out of the question to isolate free alkyl groups.

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A group of compounds known as the *metallic ketyls* also contain a trivalent carbon atom. These may be prepared in solution by the action of metallic sodium or potassium on diaryl ketones.

$$(C_6H_5)_2CO + Na \longrightarrow \underset{\text{A sodium ketyl}}{(C_6H_5)_2\underset{|}{C} - ONa}$$

They are deep blue compounds which are very reactive toward oxygen or moisture. For this reason, like hexaphenylethane, they can only be prepared in the absence of oxygen.

Odd Molecules. Spurred on by Gomberg's discovery, a number of investigators have discovered compounds in which the elements have abnormal valence. Thus a number of free radicals containing divalent nitrogen have been prepared and a few which probably have a monovalent oxygen atom. All these substances and those containing trivalent carbon atoms have been classed together as compounds whose molecules contain an uneven number of electrons and are therefore "odd molecules." These "odd molecules" are all colored in solution, have a great tendency to become "even," and thus react with a variety of reagents adding *one* atom or group to the unsaturated atom.

Aryl Derivatives of Ethylene. The simplest and most important representative of this class of compounds is **styrene,** $C_6H_5CH = CH_2$. It is found in storax, where it is probably formed by decomposition of the cinnamic compounds which are present. It may be prepared by heating cinnamic acid.

$$C_6H_5CH = CHCOOH \longrightarrow C_6H_5CH = CH_2 + CO_2$$

Styrene is prepared industrially by several methods. In one of these, ethyl benzene is dehydrogenated by heating in the gas phase at a high temperature in the presence of the oxides of certain metals.

Styrene is a very reactive unsaturated hydrocarbon. It readily polymerizes to substances of high molecular weight when heated with various catalysts. These polymers find industrial use as resins. Its largest single use is undoubtedly in the copolymerization with butadiene to form the synthetic rubber, Buna S. The production of styrene in the United States in 1944 amounted to nearly 350,000,000 lb.

Symmetrical diphenylethylene, $C_6H_5CH = CHC_6H_5$, is known as *stilbene*. It may be prepared as follows:

$$2C_6H_5CHCl_2 + 2Zn \longrightarrow C_6H_5CH = CHC_6H_5 + 2ZnCl_2$$

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Both the cis and trans forms of stilbene are known. One is a solid (mp 124°), the other an oil.

Tetraphenylethylene, $(C_6H_5)_2C = C(C_6H_5)_2$, is a substance in which the accumulation of phenyl groups around the ethylenic linkage has produced a marked effect. *It will not combine with bromine*, but does react with chlorine, forming a dichloride.

$$(C_6H_5)_2C = C(C_6H_5)_2 + Cl_2 \longrightarrow (C_6H_5)_2CClCCl(C_6H_5)_2$$

Other tetraaryl derivatives of ethylene have been prepared which will combine with neither bromine nor chlorine. These facts illustrate how a characteristic reaction of a particular linkage may disappear in a highly substituted derivative, particularly if the substituents are phenyl groups or unsaturated groups. Although tetraphenylethylene will not form a dibromide, it is reduced by hydrogen and a catalyst and combines with ozone. Therefore, toward certain reagents the reactivity of the double linkage is unimpaired.

The double linkage in tetraphenylethylene differs from that in ethylene not only by its failure to combine with bromine, but by its reactivity toward a reagent which has no effect on the aliphatic hydrocarbons. This reagent is metallic potassium which combines with tetraphenylethylene forming a highly colored metallic compound.

$$(C_6H_5)_2C = C(C_6H_5)_2 + 2K \longrightarrow (C_6H_5)_2\underset{\underset{K}{|}}{C} - \underset{\underset{K}{|}}{C}(C_6H_5)_2$$

When the addition compound is treated with bromine, the potassium atoms are removed and the unsaturated hydrocarbon regenerated. With water, the metallic atoms are replaced by hydrogen.

$$(C_6H_5)_2\underset{\underset{K}{|}}{C} - \underset{\underset{K}{|}}{C}(C_6H_5)_2 + 2H_2O \longrightarrow (C_6H_5)_2CHCH(C_6H_5)_2 + 2KOH$$

With carbon dioxide a substituted succinic acid is formed.

$$(C_6H_5)_2CKCK(C_6H_5)_2 + 2CO_2 \longrightarrow (C_6H_5)_2\underset{\underset{COOK}{|}}{C} \text{———} \underset{\underset{COOK}{|}}{C}(C_6H_5)_2$$

THE TRIPHENYLMETHANE DYES

The first synthetic dye was a triphenylmethane dye, prepared quite unintentionally in 1856. William Henry Perkin, a student in Hofmann's laboratory, undertook a study of the oxidation of aniline as part of an attempt to synthesize quinine. He obtained from the oxidation a substance whose violet-colored solutions dyed wool and silk.

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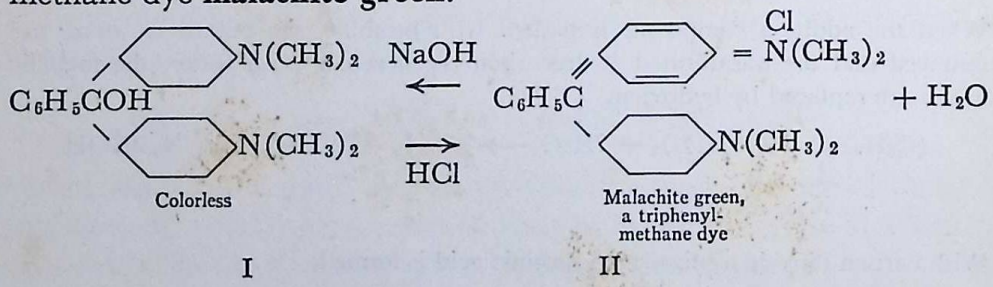
Perkin started a factory for the manufacture of the new dye, which was called *mauve*, and thus started the coal-tar dye industry.

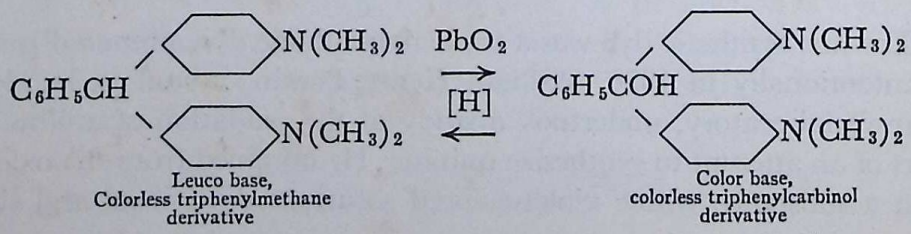
The manufacture of synthetic dyes has developed in the intervening years to an important industry. In the United States in 1940 approximately 128,000,000 lb of dyes with a value of nearly $80,000,000 were produced. The most important groups of dyes in terms of volume of production in that year were:

	Pounds
Azo dyes (p. 460)	55,700,000
Sulfide dyes (p. 440)	21,500,000
Triphenylmethane dyes	4,600,000
Anthraquinone dyes (p. 555)	3,400,000

The structure of the triphenylmethane dyes was not established until 1876, twenty years after the first one was prepared. We can understand their structure and their chemistry best by considering their relation to triphenylcarbinol and triphenylmethane. Derivatives of triphenylcarbinol in which two or three of the aromatic nuclei contain basic groups in the para positions react with hydrochloric acid to form chlorides which are not colorless nonpolar substances like triphenylmethane, but which are instead highly colored salts. These salts are the triphenylmethane dyes. For example, the colorless carbinol (I), di-*p*-dimethylamino-triphenylcarbinol, reacts with hydrochloric acid to form the hydrochloride (II), which is the triphenylmethane dye **malachite green.**



By treatment with alkali the dye is reconverted to the colorless carbinol, which is known as the *color base*. The carbinol, the color base, is readily reduced to the corresponding triphenylmethane derivative, the **leuco base.** On oxidation the leuco base regenerates the color base.



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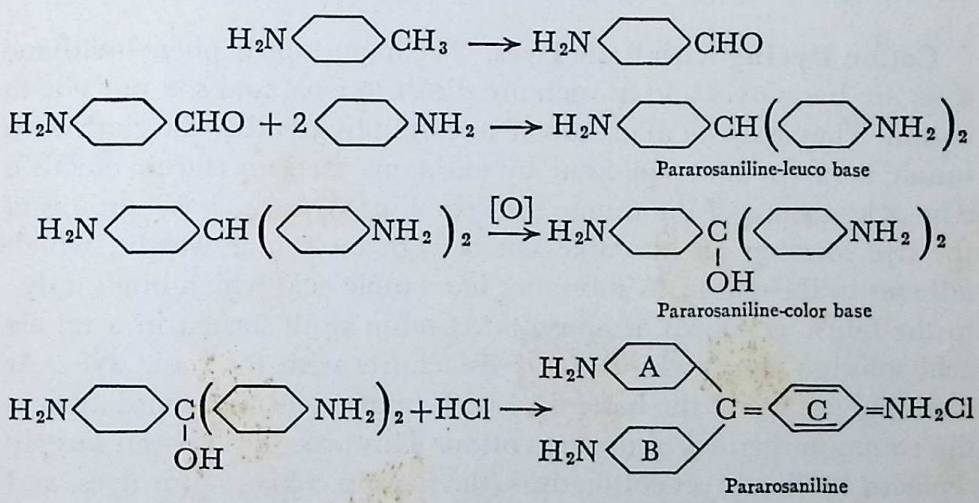
It is the relationship between the methane, the carbinol, and the dye, together with the fact that the synthesis of these dyes begins with the synthesis of the methanes, that led to the class name of *triphenylmethane dyes*. Thus the leuco base of malachite green is prepared by heating benzaldehyde and dimethylaniline in the presence of zinc chloride.

$$C_6H_5CHO + 2C_6H_5N(CH_3)_2 \longrightarrow C_6H_5CH[C_6H_4N(CH_3)_2]_2 + H_2O$$

Other Triphenylmethane Dyes. Fuchsine, or *magenta*, is a triphenylmethane dye prepared by oxidizing a mixture of aniline and the isomeric toluidines. The color base resulting from this oxidation forms the dye on treatment with hydrochloric acid. The principal constituent of magenta is the dye **pararosaniline.** It is formed by the oxidation of the para toluidine to para aminobenzaldehyde, condensation of para aminobenzaldehyde and aniline to the leuco base, oxidation of the leuco base to the color base, and conversion of the color base to the dye.



The leuco base of pararosaniline is triamino-triphenylmethane. When it is diazotized and boiled with alcohol (p. 456) the amino groups are replaced by hydrogen and triphenylmethane is formed. It was this reaction which established the structure of the triphenylmethane dyes.

Crystal violet is the hexamethyl derivative of pararosaniline, the methyl groups being substituted for the hydrogen atoms of the amino groups. This substitution changes the color from a red to a bluish violet. **Methyl violet,** which contains only five methyl groups, is of a redder shade than crystal violet, as might be expected. These dyes can be made by methylating the parent dye, but are usually synthesized

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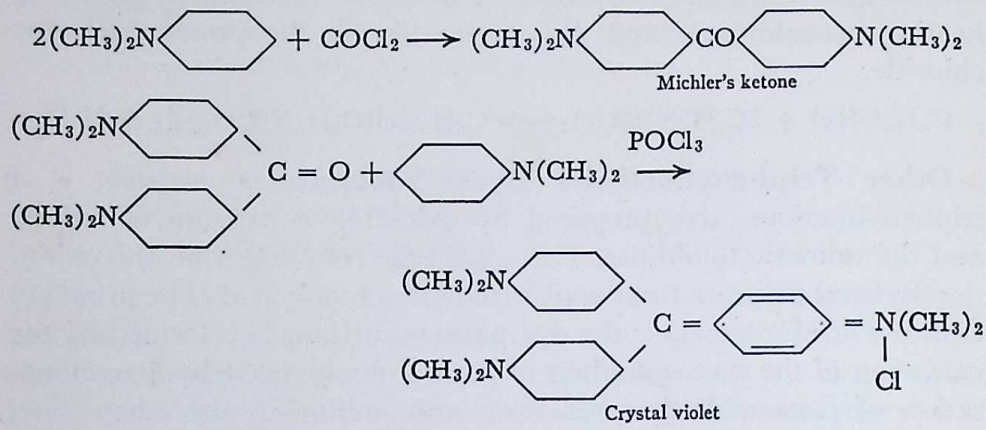
from methylated anilines. The preparation of crystal violet illustrates another method of preparing triphenylmethane dyes. A derivative of benzophenone is condensed with an aromatic amine; the substituted benzophenone is made from phosgene and dimethylaniline.



By sulfonating the triphenylmethane dyes, sulfonic acid groups may be introduced into the molecule, and thus *acid triphenylmethane* dyes are produced.

Cotton Dyeing with Basic Dyes. The important triphenylmethane dyes are basic dyes and as such are direct to wool and silk but not to cotton. They may be made direct to cotton by treating the cloth with tannic acid (p. 506), followed by antimony tartrate (tartar emetic). The acid groups of the tannic acid combine with the basic groups of the dye forming an insoluble salt of high molecular weight, which adheres to the cotton. A substance like tannic acid which binds a dye to the fabric is known as a *mordant*. Cotton cloth soaked in a tannic acid solution can be dyed very satisfactorily with the basic dyes. At one time the use of the basic dyes with tannic acid as a mordant was the common method of dyeing cotton. This process has been largely replaced by the direct cotton dyes, the ingrain colors, sulfur dyes, and the vat dyes. Although the basic dyes may be applied to cotton by the use of mordants, they are not classified as mordant dyes. This name is restricted to those dyes which are applied to fabrics by means of a metallic hydroxide as a mordant.

Color and Chemical Constitution. Most organic compounds are colorless and yield colorless solutions. Such solutions appear to our eyes to be perfectly transparent to light, but this is only because the range of light which affects our eyes is so limited (Fig. 17). All organic compounds absorb light of short wave lengths (ultraviolet light). Such absorption may be studied by means of a photographic plate and

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a spectroscope which resolves the light transmitted by the liquid. The results (Fig. 17) are called *absorption spectra*. It is found that unsaturated compounds absorb light of longer wavelength (nearer the

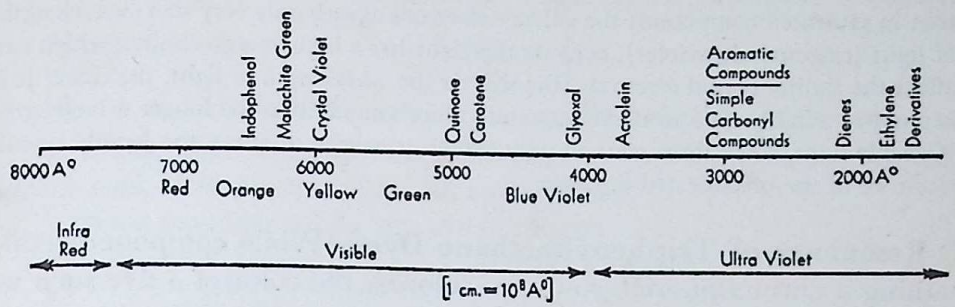
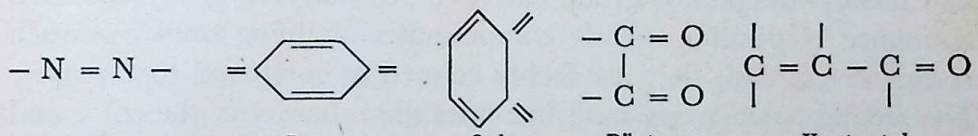


Fig. 17. Diagram showing absorption sepctra in the visible and ultraviolet regions. The approximate position of the absorption band of *longest* wave length is indicated for each compound; many compounds have absorption bands in several positions.

visible) than saturated compounds. Certain combinations of unsaturated groups cause the substance to absorb some of the light visible to the eye and the solution is then colored.

Certain unsaturated groupings are definitely associated with the absorption of visible light, and we can predict that compounds having such groupings will be colored. Such groups which confer color on a molecule are said to be *chromophoric* groups or chromophores. The following are usually regarded as important chromophores.



$-NO_2$
Nitro group in aromatic compounds

$-N=O$
Nitroso group even in aliphatic compounds

The presence of one or more aryl groups attached directly to the chromophoric group is usually essential; the introduction of such groups as $-NH_2$, $-N(CH_3)_2$, OH, OCH_3, in the aromatic nucleus intensifies the color.

Clearly any attempt to relate the color of a compound to its structure (chemical constitution) is only one aspect of the broader problem of the relation of structure and absorption spectrum. In a very rough way, we can recognize that certain groupings of atoms usually cause the absorption of a certain range of light, and can even foretell to some extent the absorption spectrum of a compound which contains several such groupings (although the effects are by no means simply additive). If the relation between structure and light absorption were completely understood, it might be

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possible to determine the constitution of many substances from an examination of their absorption spectra alone. Unfortunately, the absorption of light by the valence electrons of organic molecules is such a complex physical process that it has not been possible so far to subject it to a fundamental analysis. In a general way, it is evident that in saturated compounds the valence electrons absorb only very short wavelengths of light (extreme ultraviolet), because this light has a high energy content which can affect the tightly bound electrons (the shorter the wavelength of light, the richer it is in energy). Highly unsaturated compounds absorb in addition the longer wavelengths of visible light, since these contain only sufficient energy to affect the loosely bound electrons of the unsaturated linkages.

Resonance of Triphenylmethane Dyes. While compounds containing a chromophoric group are colored, the color of a dye such as pararosaniline is of an entirely different order of intensity from that of a simple quinone or quinone imine. Inspection of the formula of pararosaniline on page 533 shows that three arrangements of the bonds are possible according to whether the quinonoid structure is in ring A, B, or C. This situation is exactly like that already met with in the guanidinium ion, in benzene, and in other aromatic compounds. Clearly, the formulas represent resonating structures, and the triphenylmethane dyes represent systems made more stable by resonance energy. According to the wave-mechanical interpretation of the electronic theory of valence, this resonance is responsible for the fact that the triphenylmethane dyes are so highly colored. It will be seen that if only one phenyl group carries a NH_2 or NR_2 group, no such resonance is possible. While compounds containing only one such group are colored, they are feebly colored as compared to the dyes. The second basic group both increases the intensity of the color and deepens the shade (moves the band toward the red). The function of this group is to introduce the possibility of resonance. Resonance energy also makes the positive ion more stable and favors its formation from the color base.

QUESTIONS AND PROBLEMS

1. How is triphenylmethyl prepared? What properties of this and similar compounds have led chemists to formulate them as containing a trivalent carbon atom?

2. Write structural formulas for benzyl acetate; 1,1-diphenylpropanol-l, coniferyl alcohol, diphenyl *p*-tolyl carbinol, triphenylethylene, benzyl cyanide, and vanillin.

3. Show by equations the relationships between the leuco base, the color base, and the dye in any one of the triphenylmethane dyes.

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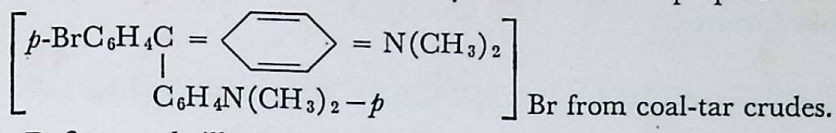
4. Write formulas for the resonating structures of triphenylmethyl, the anion of sodium triphenylmethyl, and the cation of the halochromic salt of triphenyl carbinol.

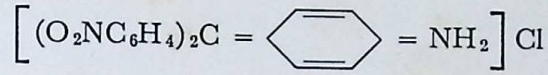
5. Outline the steps in the synthesis you would use to prepare



Br from coal-tar crudes.

6. Define and illustrate the following terms: *halochromism*, *mordant*, *metallic ketyl*, *chromophore*, *odd molecule*, *carbonium salt*.

7. What reactions would you use to convert



to triphenylmethane?

8. What types of triphenylmethane dyes are fast to wool and silk? How can these dyes be made fast to cotton?

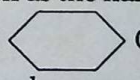
9. Indicate the steps in the synthesis of the following compounds from the coal-tar crudes and the simple aliphatic alcohols: phenyl dimethyl carbinol, ethyl cinnamate, β-phenylethyl alcohol, *m*-nitrocinnamic acid, diphenyl methyl carbinol, cinnamyl alcohol.

10. Discuss briefly the relationship between color and chemical constitution.

11. Complete and balance the following reactions:

(*a*) $(C_6H_5)_3COH + CH_3COCl$, (*b*) $(C_6H_5)_2CH_2 + [O]$,
(*c*) $(C_6H_5)_2C(OH)CH_2C_6H_5 + [O]$, (*d*) $(C_6H_5)_3COH + HCOOH$,
(*e*) $C_6H_5COOAg + CH_3CH_2Br$.

12. A hydrocarbon $C_{15}H_{14}$ on oxidation with chromic acid furnishes benzoic acid and an acid $C_8H_8O_2$. When this latter acid is esterified and the ester is treated with phenylmagnesium bromide, the product on oxidation furnishes benzophenone and benzoic acid. What is the structure of the hydrocarbon $C_{15}H_{14}$?

13. When a solution of hexaphenylethane is allowed to stand in the absence of air in the presence of various catalysts such as the halogen hydrides, the colorless crystalline hydrocarbon $(C_6H_5)_3C$  $CH(C_6H_5)_2$ is formed. Would you expect this substance to absorb oxygen? Would you expect its formation from hexaphenylethane to be reversible or irreversible? Outline a possible explanation of its formation.

14. In terms of resonance explain: (*a*) why tetraarylethylenes will combine with metallic potassium while the tetraalkylethylenes will not, (*b*) why triphenylmethyl chloride and tertiary butyl chloride behave differently when dissolved in ionizing solvents and when treated with such metals as zinc and magnesium.

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15. On treatment with strong acids many ethanes which dissociate to form odd molecules undergo an internal oxidation and reduction. The products isolated from hexaphenylethane and HCl are $(C_6H_5)_3CH$ and and $(C_6H_5)_3CCl$. Write balanced equations for the reactions you think might be involved.

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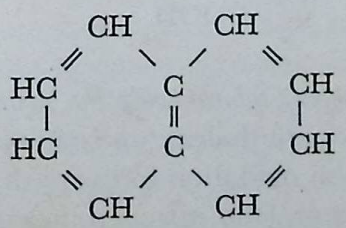
Chapter 28

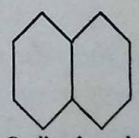
NAPHTHALENE, ANTHRACENE, AND PHENANTHRENE

Naphthalene, anthracene, and phenanthrene are present in the higher fractions which are obtained in the industrial refining of coal tar. The production of the first two substances on a large scale has resulted in their use in the manufacture of a great number of very important dyes. The three high-boiling, solid hydrocarbons, as we shall see, are aromatic compounds, but differ in certain important respects from benzene. Since there are two or more rings condensed together in the molecule of each of these substances, they are classified as condensed **polynuclear aromatic hydrocarbons.**

Naphthalene. Naphthalene, $C_{10}H_8$, is a white crystalline solid which melts at 80° and boils at 218°. It has an appreciable vapor pressure even at room temperature and readily sublimes on warming. Naphthalene has a pungent odor, and is commonly sold in flakes or balls for use as a protection against moths. It is prepared from coal tar as outlined on page 402. Since it occurs in relatively large amounts and is easily purified by distillation or sublimation, it is one of the cheap raw materials of the coal-tar chemical industry (coal-tar crudes). In 1944 almost 300,000,000 lb of crude naphthalene were produced in the United States.

Naphthalene is very similar to benzene in many of its chemical properties. It can be nitrated, sulfonated, and halogenated; it yields *two isomeric monosubstitution products* and ten isomeric disubstitution products. It is represented by the following formula which adequately accounts for these isomers.





Outline formula

The formula on the right is commonly employed. The monosubstitu-

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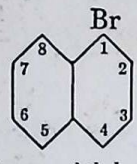
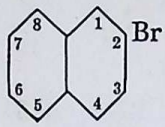
tion products are divided into two classes, designated as *alpha* and *beta*.



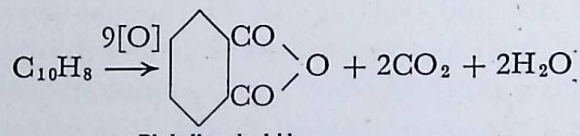
α-Bromonaphthalene or
1-Bromonaphthalene



β-Bromonaphthalene or
2-Bromonaphthalene

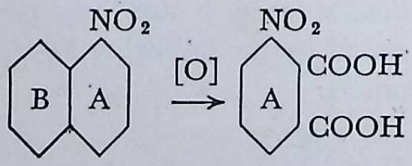
The position of substituents is also often indicated by numerals, as shown above. Clearly the 1,4,5, and 8 positions are the so-called alpha position and 2,3,6, and 7 positions are the beta positions. All the alpha positions are equivalent to each other; the same is true of the beta positions. In other words, there are two and only two mono-substitution products.

Proof of the Structure of Naphthalene. As we have seen (p. 508), naphthalene is readily oxidized to phthalic anhydride and indeed is the industrial source of the anhydride and the corresponding acid.



Phthalic anhydride

The fact that naphthalene yields phthalic acid on oxidation indicates the presence of one benzene ring in the molecule. A study of the oxidation of certain substituted naphthalenes establishes the presence of two condensed six-membered rings. The evidence is as follows: (1) by oxidizing alpha nitronaphthalene, nitrophthalic acid is produced.



This proves that the ring (marked A above) which holds the nitro group is a six-membered ring. (2) Alpha nitronaphthalene on reduction yields alpha aminonaphthalene and this on oxidation forms phthalic acid. In the first compound the substituent (the nitro group) makes the

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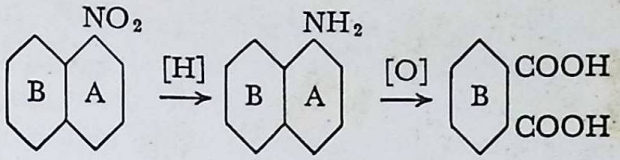
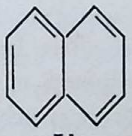
ring difficult to oxidize; in the second, the amino group facilitates the oxidation.



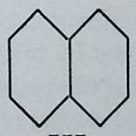
The fact that α-aminonaphthalene yields an unsubstituted phthalic acid proves that *the unsubstituted ring (marked B) in this compound and in α-nitronaphthalene is also a six-membered ring.* Therefore, it seems clear that naphthalene has *two condensed six-membered rings.* The carbon skeleton is thus established beyond question. The distribution of the hydrogen atoms about this skeleton is determined by the fact that there are two, and only two, monosubstitution products. Only a symmetrical distribution of the eight hydrogen atoms would lead to such a situation.

Like the benzene problem, the question of formulating the unsaturation of naphthalene has been much discussed. Like benzene, naphthalene is a resonance hybrid; unlike benzene and like butadiene, one contributing form to the hybrid (II, below) is more important than the others. We can either, therefore, write a noncommittal outline formula such as III, or use formula II which is more closely representative of the chemical behavior of naphthalene than is either I*a*, I*b*, or III. We shall use formula II. The detailed reasons for preferring this formula are to be found in the reactions of naphthalene described in the following pages, and they will be summarized on page 545.

I*a*


I*b*

II


III

Addition Reactions of Naphthalene. Naphthalene has a more pronounced unsaturated character than benzene or its alkyl derivatives. Its oxidation to phthalic acid is one example of this. Naphthalene can be reduced by sodium and alcohol, a reagent which will not attack benzene. Four hydrogen atoms are taken up in pairs. The tetrahydronaphthalene now behaves like a dialkyl benzene and is very resistant to further hydrogenation.

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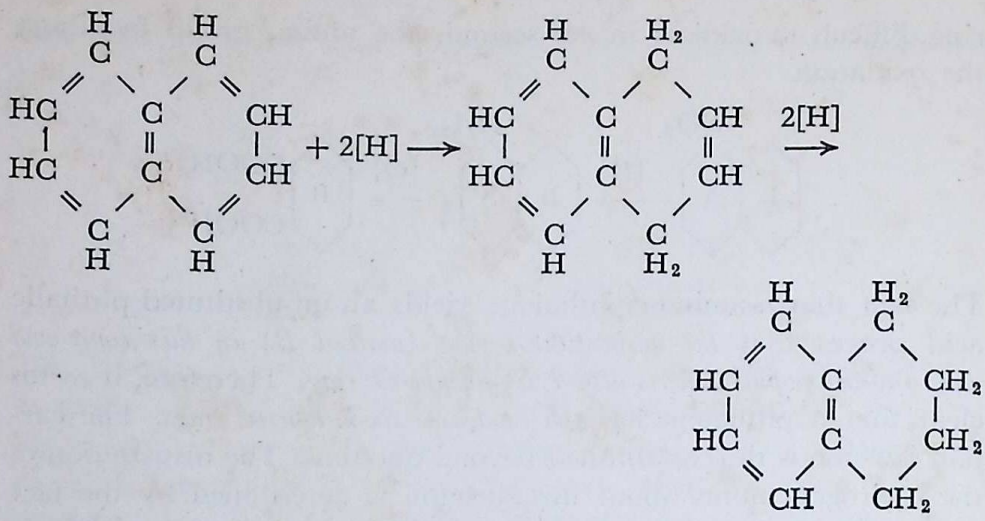
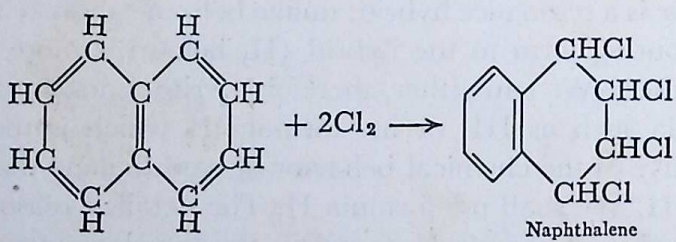


Naphthalene combines with *four* chlorine atoms more easily than benzene forms a hexachloride (p. 407). The resulting naphthalene tetrachloride is clearly a benzene derivative just as is the tetrahydro compound mentioned in the preceding paragraph.



Naphthalene tetrachloride

On heating naphthalene tetrachloride, hydrochloric acid is eliminated from the molecule and a mixture of chloronaphthalenes results. These are *substitution products* of naphthalene, of course. Such facts led many chemists to believe that all substitution reactions in aromatic chemistry (benzene derivatives included) are preceded by direct addition of the reagent to the double linkage of the aromatic compound. Careful studies of the rates of such reactions indicate clearly, however, that this is not the mechanism of the usual aromatic substitution reactions.

Energy Relationships in the Addition Reactions of Naphthalene. Whereas the addition of two hydrogen atoms to benzene would be endothermic by about 6 kg-cal, the addition of two hydrogen atoms to naphthalene evolves some 6 to 9 kg-cal. This is small as compared with the heat evolved in the hydrogenation of a simple open-chain ethylenic linkage, but it is sufficient to correspond to the observation that the addition reaction does go. The resonance energy of naphthalene is greater than that of benzene (74 kg-cal as compared with 36 kg-cal), but dihydro- and tetrahydronaphthalene are stabilized by resonance to about the same extent as is benzene. The addition of two or four hydrogen atoms to naphthalene does not lead to products

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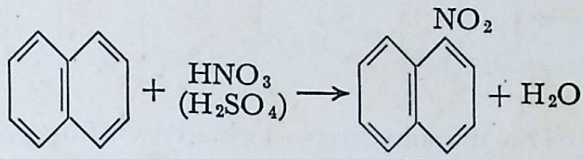
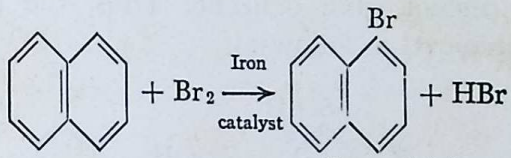
with little or no resonance energy as it does with benzene; instead it leads to products having only somewhat less resonance energy than naphthalene itself.

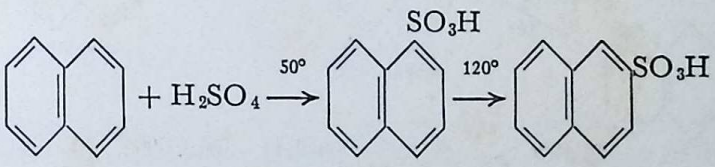
Substitution Reactions of Naphthalene Derivatives. The typical aromatic reactions of benzene are also characteristic of naphthalene. Halogenation and nitration of naphthalene produce the alpha isomer. Sulfonation also goes in the same way, but at a higher temperature the alpha isomer rearranges to the beta.



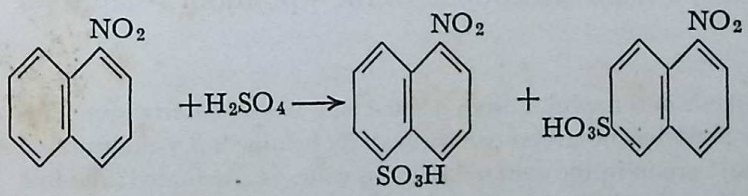
α-Nitronaphthalene



α-Bromonaphthalene



The introduction of a second substituent into the naphthalene ring follows the same general principles which we found to apply to benzene. The nature of the group already present determines the position of the entering group. As a general rule, meta orienting groups (NO_2, SO_3H) cause the entering group to go into the other ring; this is in accord with the fact that the presence of such groups in a nucleus makes the introduction of a second substituent more difficult. Apparently the retarding influence of a meta orienting group is confined to the ring to which the group is attached. The ortho and para orienting groups (OH and NH_2) in the alpha position direct the incoming group to the 2 or 4 position (equivalent to the ortho and para positions in benzene). The same groups in the beta position favor the introduction of the second substituent in the alpha position or in the other ring. The following examples will serve as illustrations.



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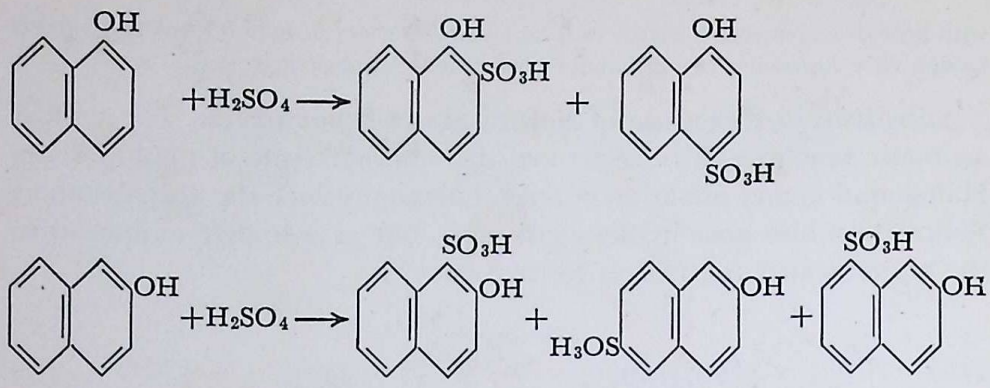
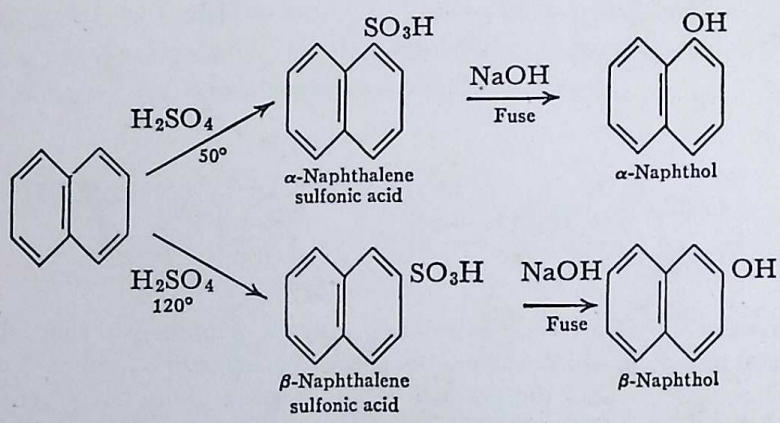


The Naphthols. The monohydroxy derivatives of naphthalene may be prepared from naphthalene by a process identical with that used for obtaining phenol from benzene. Thus, the two isomeric naphthols may be prepared as follows:



Alpha naphthol, $C_{10}H_7OH$ (α), and **beta naphthol,** $C_{10}H_7OH$ (β), are solids melting at 95° and 122° and boiling at 279° and 285° respectively. They resemble phenol in their general reactions; they are weak acids, soluble in sodium hydroxide solution but not in sodium bicarbonate solution. They are prepared in large quantities for use in the manufacture of azo dyes (p. 460). They readily couple with diazonium salts; α-naphthol couples in the 4 position, β-naphthol in the 1 position.

An interesting synthesis of a naphthol from a side-chain benzene derivative illustrates how readily the naphthalene structure is formed. By heating a β,γ-unsaturated acid which has a phenyl group in the gamma position, water is eliminated; the first product of the reaction is probably the ketonic form of α-naphthol, which immediately shifts to the enolic form.

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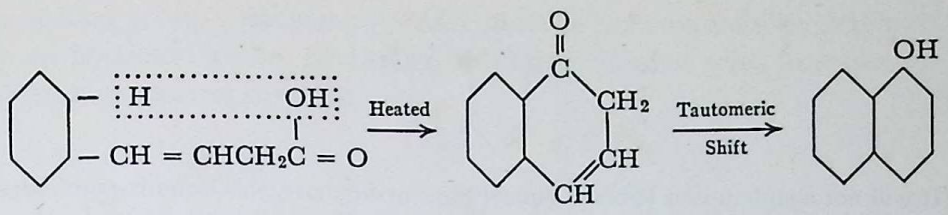
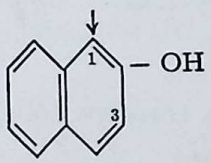


γ-Phenyl-Δβ, γ-butenoic acid

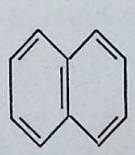
Unknown ketonic form of alpha naphthol

The ketonic forms of the naphthols are unknown.

Concerning the 1 and 3 Positions in Beta Substituted Naphthalenes. At first sight it may seem remarkable that in the sulfonation of beta naphthol, no monosulfonated product is formed with a sulfonic acid group in position 3. By analogy with phenols one would expect that both ortho positions to the hydroxyl group in beta naphthol would be reactive. As a matter of fact, position 3 is very different from position 1. This is brought out most strikingly by a consideration of the coupling of naphthols with diazonium salts. Beta naphthol couples exclusively in the alpha position (1) and if this position is occupied by some atom or group other than hydrogen,



no coupling occurs even under the most drastic conditions. Though preferential coupling between two ortho positions in phenols is known, there is no analogy in the benzene series for this failure of the coupling reaction to proceed when an ortho position to OH is free. This and similar facts lead one school of chemists to write the formula of beta naphthol with the linkages as indicated above. It is argued that if any of the isomers with the double linkage between atoms 2 and 3 were present, coupling should proceed in the 3 position as with phenols. Extrapolating from the hydroxy compound to the hydrocarbon, such chemists prefer to write a naphthalene formula with all the double linkages shown and arranged as follows:



A Useful Naphthalene Formula. We have seen that there is no advantage to be gained from writing the double bonds into the formulas for benzene compounds. With naphthalene, however, there is no doubt that as a matter of convenience there is much to be said for adopting such a practice. This is even more true of the still more complicated hydrocarbons with three rings. The formula above, as compared to an ambiguous outline formula, or a centric formula, or one with oscillating linkages, enables the reader to remember such facts as the failure of 2,7-dihydroxynaphthalene to couple when both the 1 and 8 positions are occupied.

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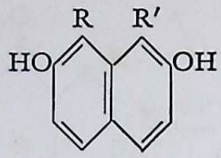
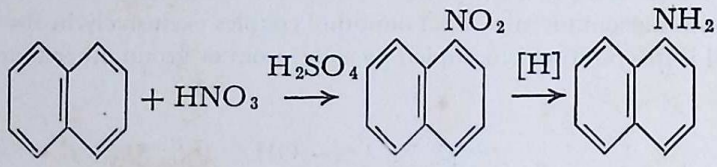


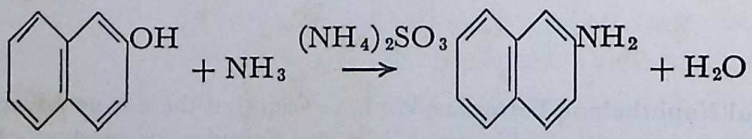
(It will not couple unless R or R′ equals H.) Furthermore, this formula emphasizes the fact that, while the affinity of naphthalene for hydrogen is much less than that of ethylene derivatives, it is much greater than that of benzene. In the reduction of naphthalene a pair of hydrogen atoms is added in either the 1,2 or 1,4 positions corresponding to 1,2 and 1,4 addition to conjugated open-chain compounds (p. 70).

The Naphthylamines. The alpha naphthylamine is readily prepared from naphthalene by nitrating the hydrocarbon and then reducing the nitro compound. The process is thus exactly like that used for the preparation of aniline from benzene.



Alpha naphthylamine is a colorless solid which melts at 50° to a liquid which boils at 300°.

The beta isomer cannot be readily prepared by a similar set of reactions, as the nitration of naphthalene yields only the alpha isomer. Fortunately, however, it is possible to replace the hydroxyl group by the amino group much more readily in the naphthalene series than in the benzene series. This replacement is brought about by heating the naphthol with aqueous ammonia and ammonium sulfite. The conversion of a naphthol to a naphthylamine and the reverse process are known as the *Bucherer reaction.* Since beta naphthol is easily prepared from naphthalene as we have just seen, beta naphthylamine is made from it by this reaction.



Beta naphthylamine melts at 112° and boils at 294°. Both amines are insoluble in water, but are soluble in aqueous solutions of mineral acids since they readily form soluble salts with acids. The amino group is very similar in its characteristics to the amino group of aniline. Thus, the naphthylamines can be diazotized to form diazonium salts.

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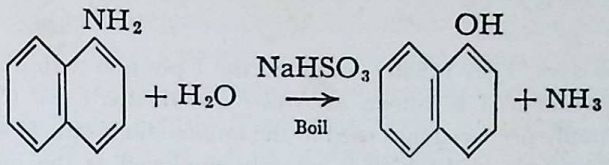
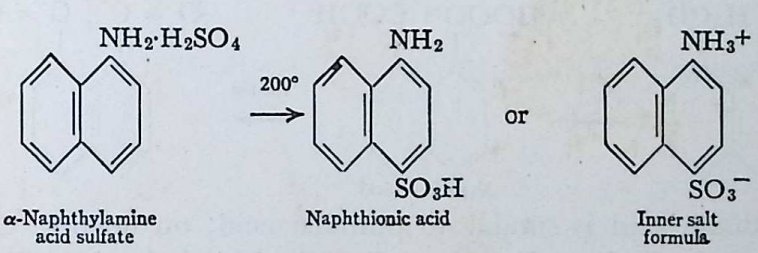
An amino group attached to a naphthalene nucleus may be replaced by an hydroxyl group by boiling a naphthylamine with an aqueous solution of sodium bisulfite.



Sulfonated Naphthylamines and Naphthols. A very important group of intermediates for the manufacture of azo dyes are the sulfonated naphthols and naphthylamines. The sulfonic acid group is introduced into the molecule for the purpose of making the compounds *soluble in water;* this water solubility survives even in the complicated azo dye molecule which is subsequently made from such a compound by a coupling reaction.

Naphthionic acid is the naphthalene analog of sulfanilic acid (p. 445). Like the latter compound, it is prepared by baking the acid sulfate salt of the corresponding amine.



It very closely resembles sulfanilic acid and undoubtedly is an inner salt. It is practically insoluble in water but is soluble in sodium carbonate solution because of the formation of the very soluble sodium salt. The aromatic amino sulfonic acids which contain the same number of amino and sulfonic acid groups in the molecule are nearly insoluble in water because they are really inner salts; they are isolated in this form. The introduction of another sulfonic acid group in the molecule makes the compound soluble in water like any other sulfonic acid, and such soluble sulfonic acids are usually isolated as sodium salts.

The **beta naphthol sulfonic acids** are prepared by sulfonating beta naphthol. (The orientation in this reaction has already been discussed.) Depending on the conditions, one, two, or three sulfonic acid groups are introduced. The sulfonated naphthols are very soluble in water and are usually isolated as the corresponding sodium salts by a "liming out" process (p. 426). The compounds which are thus prepared and sold are actually the sodium salts though they are frequently spoken of erroneously as though they were the free acids.

The *sodium salt of beta naphthol-3,6-disulfonic acid* is known as *R salt;* while *sodium beta naphthol-6,8-disulfonate* is called *G salt.* These substances are used in the prepara-

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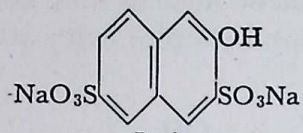
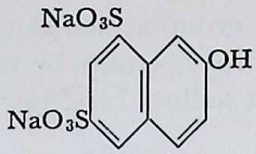


R salt



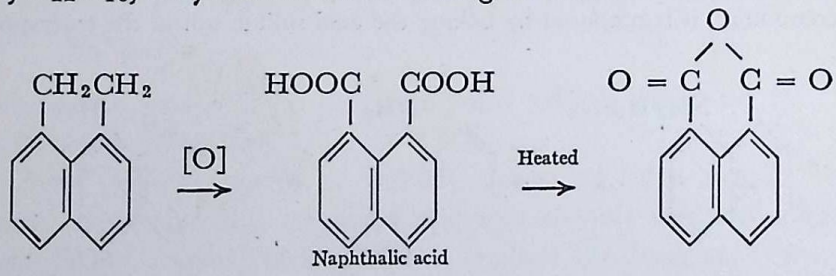
G salt

tion of many azo dyes. They readily couple in the 1 position with diazonium salts.

1-Naphthol-4-sulfonic acid is known as *Neville and Winther's acid* (N. & W. acid), although it is actually prepared and used as the monosodium salt. **H acid** is 1-amino-8-naphthol-3,6-disulfonic acid which is actually employed as the monosodium salt (though the latter is often referred to as *H acid*). It is used in the manufacture of many important dyes.

Another dye intermediate of importance is 2-hydroxynaphthalene-3-carboxylic acid. It is made by the Kolbe synthesis from beta naphthol. The carboxylic group enters the 1 position but on heating migrates to the 3 position.

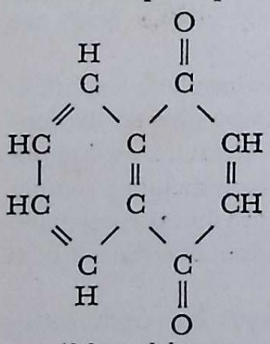
Naphthalic Acid. This dibasic acid derived from naphthalene has two carboxyl groups in the 1 and 8 positions. Two such groups are said to be in the *peri* position. The acid is formed by oxidizing acenaphthene, $C_{12}H_{10}$, a hydrocarbon occurring in small amounts in coal tar.



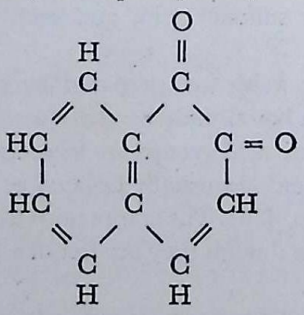
Naphthalic acid

Naphthalic acid is similar to phthalic acid; on heating the free acid, water is eliminated and a cyclic anhydride is formed. Evidently groups in the 1,8 positions in naphthalene have similar spatial relations to those in the 1,2 positions in benzene. This is readily seen in a model in which both rings of the naphthalene nucleus are in the same plane.

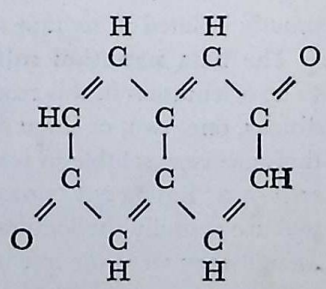
Naphthoquinones. Three quinones related to naphthalene are known. They are known as *alpha naphthoquinone*, *beta naphthoquinone*, and *amphi naphthoquinone*.



Alpha naphthoquinone



Beta naphthoquinone



Amphi naphthoquinone

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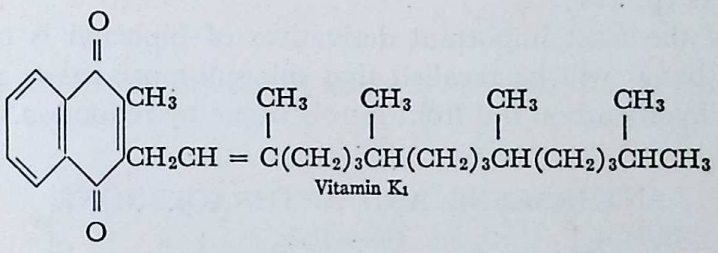
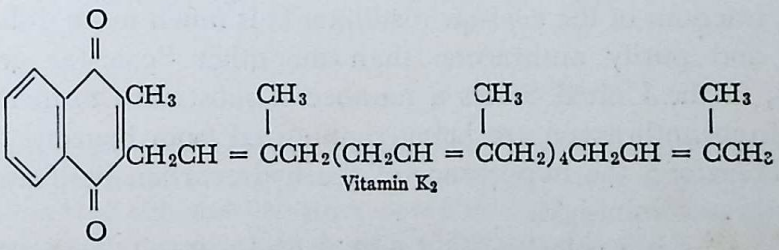
The relationship between the naphthalene quinones and the corresponding dihydroxy derivatives of naphthalene is exactly analogous to the relation between quinone and hydroquinone (p. 466). The naphthoquinones are prepared by oxidizing the corresponding dihydroxy compounds or corresponding aminohydroxy derivatives of naphthalene. Like the benzoquinones, the naphthoquinones are colored solids. The amphi and beta compounds are orange, the alpha quinone is yellow.

The alpha and beta naphthoquinones are to be regarded as related to 1,4 and 1,2 benzoquinone respectively, as naphthalene is related to benzene. The addition of another aromatic ring in this way has lowered the affinity of the quinone for hydrogen, and the corresponding dihydroxy compounds are thus oxidized by reagents which are not powerful enough to oxidize the corresponding benzene derivatives (i.e., hydroquinone and pyrocatechol). The dehydrogenation of 2,6-dihydroxynaphthalene to amphiquinone is more like the oxidation of hydroquinone, and in a sense this compound may be regarded as the true naphthalene analog of para benzoquinone.

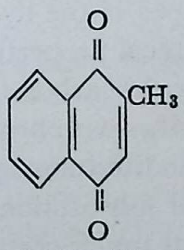
Vitamin K. Two naturally occurring antihemorrhagic factors, Vitamins K_1 and K_2, are dialkyl derivatives of alpha naphthoquinone, and 2-methyl-1,4-naphthoquinone is also a powerful antihemorrhagic agent.



Vitamin K_1



Vitamin K_2



2-Methyl-1,4-naphthoquinone

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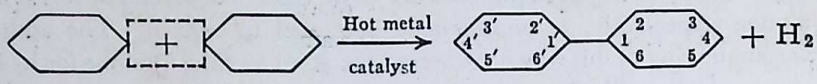
BIPHENYL

The hydrocarbon, biphenyl, has already been referred to a number of times. It can be prepared by the Wurtz-Fittig reaction from bromobenzene (p. 414), but is now prepared industrially merely by bringing benzene vapors in contact with a hot metal.



Biphenyl is a colorless crystalline solid which melts at 76° and boils at 254°; its high boiling point and great stability on heating have made it useful where a high-boiling liquid is required.

Derivatives of Biphenyl. Biphenyl is very similar to benzene in it reactions, as would be expected from its structure. Chloro, bromo, and nitro derivatives can be prepared by the usual procedures. The highly chlorinated biphenyls have been manufactured for use as plasticizers (p. 514).

One of the most important derivatives of biphenyl is benzidine (p. 462) but it will be recalled that this substance is not prepared from the hydrocarbon but from nitrobenzene by reduction.

ANTHRACENE AND ANTHRAQUINONE

Anthracene. This hydrocarbon, $C_{14}H_{10}$, is present in the high-boiling fractions of the coal-tar distillate. It is much more difficult to isolate and purify anthracene than the other "coal-tar crudes." Indeed, in the United States a number of substances formerly prepared from anthracene are being synthesized from benzene derivatives. Therefore, the importance of the hydrocarbon itself as a raw material has diminished.

Anthracene is a colorless solid with a bluish fluorescence which is also weakly shown by solutions of the hydrocarbon. It melts at 216° and boils at 342°. In its chemical properties, it more nearly resembles an open-chain unsaturated hydrocarbon than does even naphthalene. For example, it readily combines with bromine or chlorine, is reduced to a dihydroanthracene by sodium amalgam, and is easily oxidized. At the same time, the typical substitution reactions of aromatic compounds can be brought about under certain conditions. The formula which best expresses the behavior of this interesting compound is the following, which is often written in outline as shown on the right.

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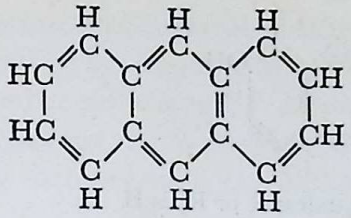
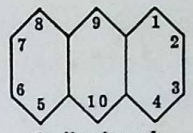
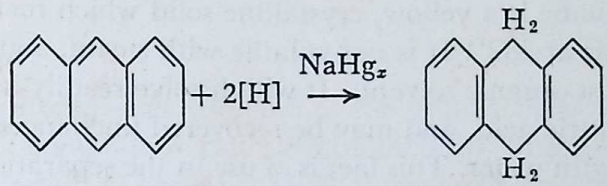




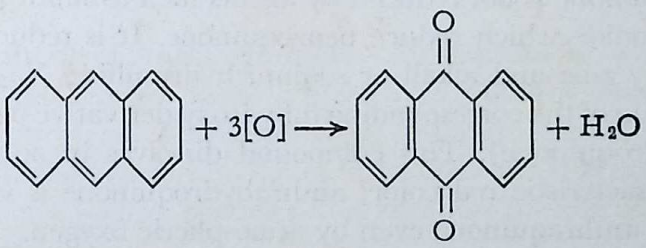
Outline formula

The method of numbering the ring is shown above. The two carbon atoms in the middle ring (9 and 10) are the points at which the anthracene molecule readily adds two atoms or groups. This may be represented by the reduction of anthracene to dihydroanthracene as follows:



Dihydroanthracene

The oxidation to 9,10-anthraquinone is to be written as follows:



9,10-Anthraquinone

The arrangement of double bonds in anthracene as written above is preferable to other arrangements and to a noncommittal outline formula for a variety of reasons. The left-hand half of the formula written above is essentially an ortho quinone (p. 469). It is therefore not surprising that the ends of this system (atoms 9 and 10) are the points of attachment of atoms or groups in addition reactions. The reduction of anthracene by 1 mole of hydrogen is thus analogous to the reduction of an ortho quinone. The affinity of anthracene for one pair of hydrogen atoms in this position appears to be greater than the affinity of naphthalene for hydrogen and begins to approach that of ethylenic derivatives. (Estimated 15 kg-cal of heat evolved as compared with 6 to 9 for naphthalene, −6 for benzene, and 28 to 30 for ethylene compounds.) This illustrates the fact that, as far as the energy relations of addition reactions are concerned, there is no sharp line separating aromatic from aliphatic compounds. 2,6-Dihydroxyanthracene will not couple with diazonium salts when the 1 and 5 positions are both blocked. If these positions are free, coupling in these places occurs. These facts are expressed by the anthracene formula employed in this chapter.

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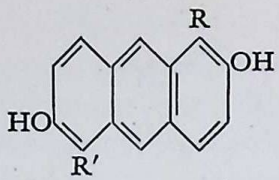
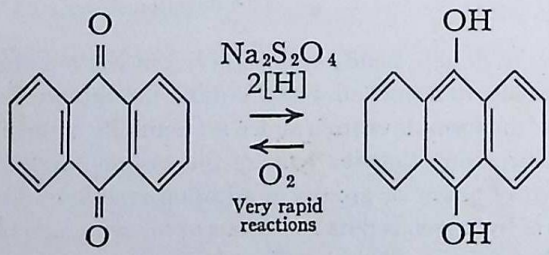


Will not couple unless R or R′ is H

Anthraquinone. The compound formed by the oxidation of anthracene is known as *anthraquinone*. It is very much more important than anthracene. A number of the most useful dyes are prepared from anthraquinone, and this compound is, therefore, one of the most important coal-tar intermediates.

Anthraquinone is a yellow, crystalline solid which melts at 284° to 285° and boils at 382°. It is not volatile with steam, and is difficultly soluble in most organic solvents. It will dissolve readily in warm, concentrated sulfuric acid, and may be recovered unchanged by diluting the solution with water. This fact is of use in the separation of anthraquinone from impurities, which are made water-soluble by such treatment.

Anthraquinone is not reduced by agents such as sulfurous acid and hydrogen iodide which reduce benzoquinone. It is reduced rapidly, however, by zinc and alkali or sodium hydrosulfite, $Na_2S_2O_4$, with the formation of the corresponding dihydroxy derivative of anthracene (anthrahydroquinone). This compound dissolves in aqueous alkali with a characteristic red color; anthrahydroquinone is very rapidly oxidized to anthraquinone even by atmospheric oxygen.



The relation between anthraquinone and its reduction product is exactly like that between quinone and hydroquinone (p. 468).

Sodium hydrosulfite (also known as *sodium hyposulfite* but not to be confused with hypo, $Na_2S_2O_3$) is a powerful reducing agent as compared with sulfurous acid, hydrogen iodide, or stannous chloride, but is not so powerful as a metal since it will not liberate free hydrogen. It is much used in the industry in the reduction of dyes. When it acts as a reducing agent it is oxidized according to the following equation:

$$Na_2S_2O_4 + 2H_2O \longrightarrow 2NaHSO_3 + 2[H]$$ Taken up by oxidizing material

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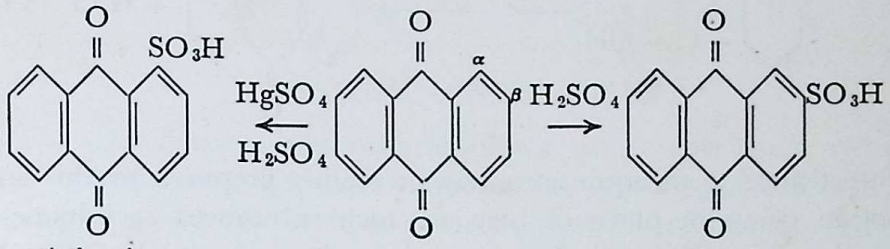
Substitution Products of Anthraquinone. Anthraquinone may be sulfonated by heating it with sulfuric acid (usually with the addition of some fuming sulfuric acid). Under ordinary conditions the sulfonic acid group enters the 2 position (known as the *beta position*); in the presence of mercury salts, the alpha sulfonic acid is produced.

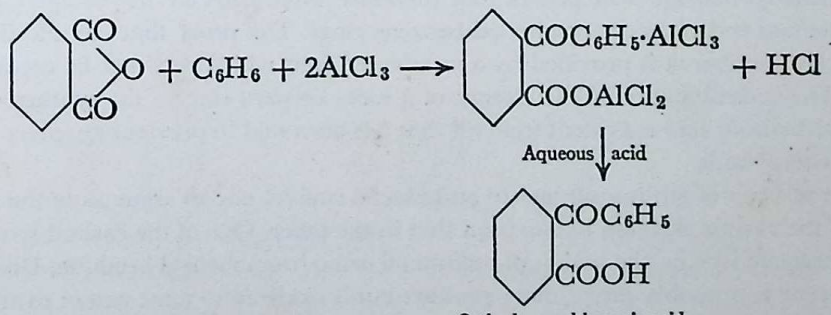


α-Anthraquinone sulfonic acid

β-Anthraquinone sulfonic acid

From these sulfonic acids (isolated in the usual way as sodium salts), the hydroxyl compounds can be obtained by fusion with sodium hydroxide. Certain of these hydroxyl compounds are important dyes and will be considered later. The amino derivatives of anthraquinone may be prepared by heating the hydroxy compounds with ammonia under pressure.

The Synthesis of Anthraquinone. Anthraquinone is now manufactured in the United States largely from phthalic anhydride and not from anthracene. This synthesis of anthraquinone is carried out in two steps: the first is a modified Friedel-Crafts reaction (p. 410), the second, a so-called condensation reaction in which the middle ring is closed.



Ortho benzoyl-benzoic acid

It will be noted that, like certain other examples of the Friedel-Crafts reaction which we have considered, an *acid anhydride* is here used instead of an acid chloride (p. 491). Two moles of aluminum chloride are employed and the product of the reaction is an aluminum salt which must be decomposed with acid to give the desired **ortho**

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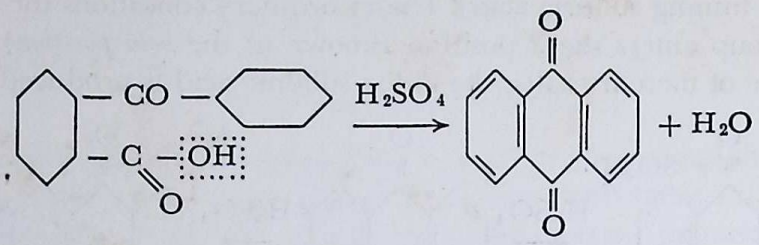
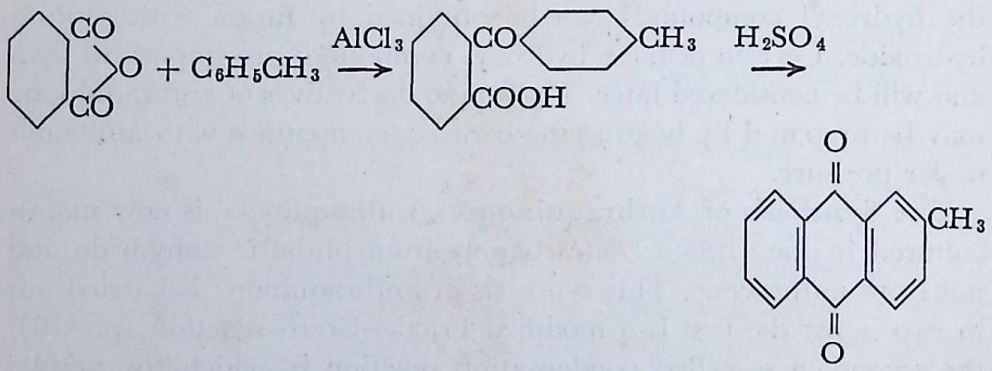
benzoyl-benzoic acid. This substance when treated with concentrated sulfuric acid forms anthraquinone.

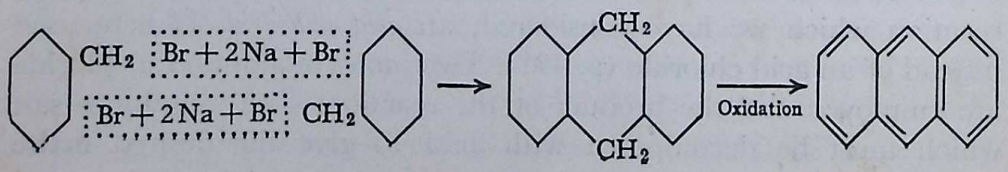


Substituted anthraquinones may be readily prepared by this same reaction using in place of benzene such substances as toluene or chlorobenzene. Beta-substituted anthraquinones are obtained; the intermediate ortho benzoyl-benzoic acids are substituted in the para position.



Structure of Anthraquinone and Anthracene. The synthesis of anthraquinone from benzoyl-benzoic acid proves that there are three rings in the compound and that the two end rings are condensed benzene rings. The proof that the middle ring is also six-membered is provided by a number of facts which need not be considered here. The improbability of the closure of a meta or para ring in the synthesis from benzoyl-benzoic acid is evident from all that has been said in previous chapters about cyclic compounds.

The relation of anthraquinone to anthracene enables one to argue as to the structure of the carbon skeleton in one from that in the other. One of the earliest syntheses of anthracene was by the action of sodium on ortho bromobenzyl bromide. Dihydroanthracene is probably the primary product but is oxidized to some extent to anthracene. This method of preparation afforded evidence of the correctness of the supposition that there were three condensed benzene rings in the molecule.



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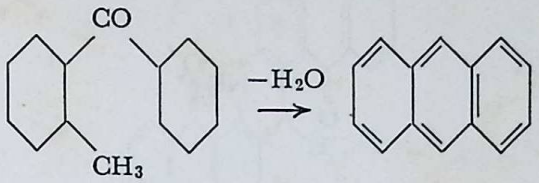
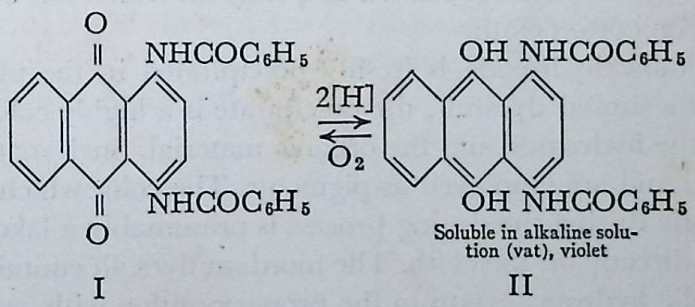
Another simple synthesis of anthracene is by means of the **Elbs reaction.** When ortho methylbenzophenone is heated, water is eliminated intramolecularly.



ANTHRAQUINONE DYES

The dyes derived from anthraquinone are of two kinds, vat dyes and mordant dyes. The anthraquinone vat dyes are applied to fabrics by a process that depends on the reduction of an insoluble quinone to an alkali soluble hydroquinone and the subsequent oxidation of the hydroquinone to the quinone, the reactions shown on page 468. The anthraquinone mordant dyes are applied to fabrics in the form of a chelate metallic derivative of the dye which is formed in the fabric.

Algol Red. A Vat Dye. Perhaps the simplest anthraquinone vat dye is algol red (I), the dibenzoyl derivative of 1,4-diaminoanthraquinone. It is a scarlet-red dye which, on treatment with an alkaline reducing agent, is reduced to the alkali soluble anthrahydroquinone (II). The reduction is carried out in a vat (hence the name *vat dye*), and the yarn or cloth is passed through the solution of the reduced dye. On exposure to the air for a short time, the reduced dye is reoxidized by atmospheric oxygen to form the original insoluble dye. The dye, thus regenerated in the fiber of the cloth, is very fast to washing.



The "vats" prepared from the anthraquinone vat dyes are usually highly colored.

The first anthraquinone vat dye was prepared in 1901 by fusing β-aminoanthraquinone with alkali. Two molecules condensed together. The product is known as *indanthrene blue*. The anthraquinone

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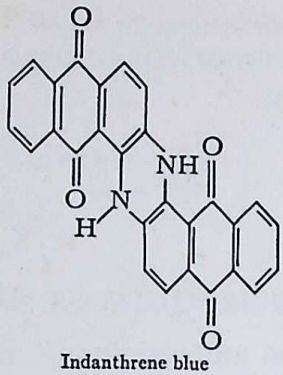

Indanthrene blue

structure is intact in this dye, and it is reduced in the vat to an anthrahydroquinone derivative which is soluble in alkali.

The anthraquinone vat dyes are highly valued for use on cotton. They are extremely fast to washing and to light. They are expensive to manufacture and are sold at a high price.

Alizarin. A Mordant Dye. The mordant dyes are themselves incapable of dyeing fabrics, but if the cloth is impregnated with a **metallic hydroxide** and boiled with a suspension of the dye, a permanent color is formed. The color varies with the nature of the metal. The process is usually carried out by soaking the cloth in a solution of the acetate of the metal. On boiling the fabric, the acetate is hydrolyzed and the metallic hydroxide thus precipitated on the fiber, where it combines with the dye. The salts of aluminum, iron, chromium, and tin are commonly employed. Alizarin, 1,2-dihydroxyanthraquinone, is one of the important mordant dyes; with an aluminum mordant, it gives the color known as *Turkey red* which has been much employed on cotton cloth.

If a metallic hydroxide is freshly precipitated in the presence of alizarin or a similar dyestuff, the precipitate is a highly colored compound of the hydroxide and the organic material. Such materials are called *lakes* and are employed as pigments. The color which develops on the fabric during the dyeing process is presumably a lake which is generated directly on the cloth. The mordant dyes all contain at least one phenolic hydroxyl group in the proper position with respect to a carbonyl group to form a chelate ring. The lakes are to be regarded as complex chelate metal salts of the dyes.

Alizarin occurs in the madder root as a glucoside. It is now prepared from anthraquinone. The latter is sulfonated and the sodium salt of the sulfonic acid fused with sodium hydroxide. Not only is one hy-

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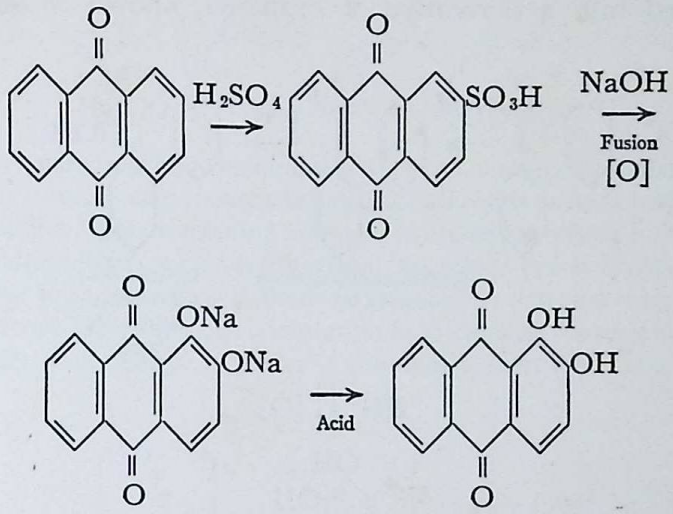
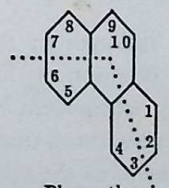
droxyl group thus introduced into the molecule, as would be expected, but a second is also formed by the oxidizing action of the atmosphere (see phloroglucinol, p. 471)



Phenanthrene. An isomer of anthracene is known as *phenanthrene;* it also occurs in coal tar and may be isolated from the higher fractions. Although it may be thus obtained without much difficulty, it is not usually separated because neither it nor its derivatives have been found to be of sufficient commercial value to warrant the expense of their manufacture. Unlike anthracene derivatives (or rather anthraquinone derivatives), the phenathrene series of compounds seem to possess no characteristic which makes them more valuable industrially than the more accessible benzene and naphthalene compounds.

In phenanthrene three benzene rings are condensed together in what may be considered an angular manner as contrasted with the linear condensation in anthracene.



Phenanthrene

Phenanthrene, like anthracene, is a colorless solid with a slight fluorescence. It melts at 100° and boils at 340°. On oxidation, it is attacked at the 9,10 position and yields 9,10-phenanthraquinone. This substance is a typical quinone in regard to its relation to its

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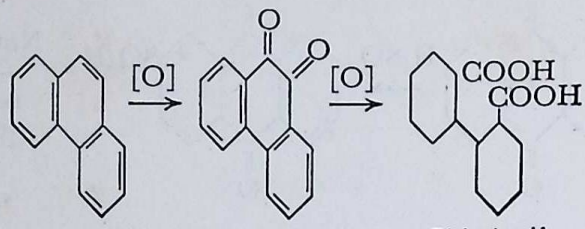
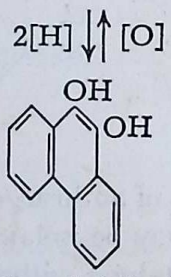
reduction product, but it is reduced by less powerful reagents than those required to reduce the isomeric 9,10-anthraquinone.

On further oxidation with chromic acid, phenanthraquinone is transformed into a derivative of biphenyl, known as *diphenic acid.*



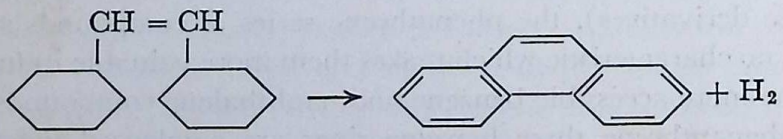
9, 10-Phenanthraquinone

Diphenic acid (2, 2′-biphenyl-dicarboxylic acid)



9,10-Phenanthrahydroquinone

Phenanthrene is formed when the vapors of stilbene (p. 530) are passed through a red-hot tube.



(At first sight the formula for phenanthrene written above seems to be different from that written on page 557, but the one becomes identical with the other by rotating the page.)

The distribution of the double linkages in the phenanthrene formulas written above corresponds to the modes of reaction of this hydrocarbon and its derivatives. The 9,10 position is very nearly equivalent to an open-chain double bond. Hydrogen can be added (1 mole) in the usual manner; the heat evolved in this reaction is estimated to be about the same as in the addition to anthracene. Bromine adds to form a dibromide, but the reaction is reversible and does not run to practical completion under the usual conditions.

Other Condensed Aromatic Hydrocarbons. A number of other polynuclear aromatic hydrocarbons occur in coal tar or may be prepared synthetically. Not only six-membered carbon rings, but also five-membered rings are found condensed with the benzene ring. Thus indene and fluorene are analogous to naphthalene and

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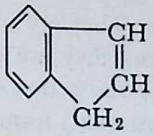
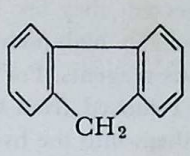
anthracene except that a five-membered ring replaces a six-membered ring. They both occur in coal tar.

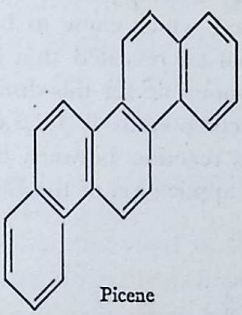


Indene

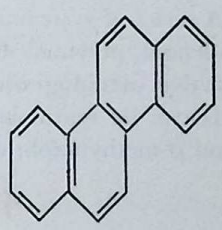


Fluorene

One of the hydrocarbons containing a very large number of condensed rings is **picene,** $C_{22}H_{14}$, which occurs in some varieties of coal tar. It melts at 364°. **Chrysene,** $C_{18}H_{12}$, is another highly condensed aromatic hydrocarbon which is found in coal tar. When obtained from coal tar, it forms beautiful golden-yellow crystals. The color, however, is due to an impurity which can be removed by repeated recrystallizations. Chrysene melts at 255°. Chrysene is important in elucidating the structure of certain sterols and bile acids (Chap. 30), since it is obtained from them as a degradation product.

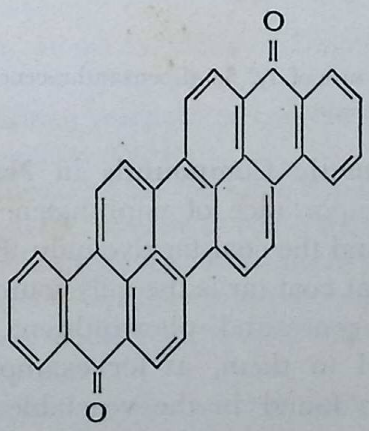


Picene



Chrysene

A number of important vat dyes have been synthesized which contain eight or nine benzene rings condensed together with but two carbonyl groups. They may be regarded as the quinones of polynuclear aromatic hydrocarbons. On reduction, they pass into alkali-soluble hydroquinones which are easily oxidized by the air. The formula of one of these substances is of interest because of its very great complexity.



Indanthrene violet (nine rings)

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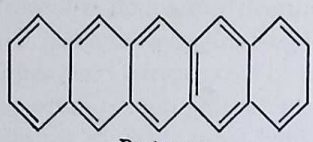
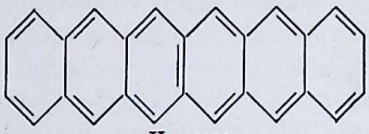
These substances are of very high molecular weight and very high carbon and low hydrogen content. (Indanthrene, C = 89.6; O = 6.8; H = 3.6 per cent.) Therefore, as would be expected, they are insoluble in practically all solvents, are nonvolatile, and have extremely high melting points. They are tremendously resistant to attack by even vigorous reagents. For this reason, they are the fastest of all known dyes, and can only be removed from a fabric by the action of an alkaline reducing agent which converts them into the hydroquinone (vat) form.

Two synthetic condensed polynuclear hydrocarbons, pentacene and hexacene, are of interest as higher homologs of a series of which the first three members are benzene, naphthalene, and anthracene. Pentacene and hexacene are colored blue and green, respectively. They are highly reactive in addition reactions and are easily oxidized.

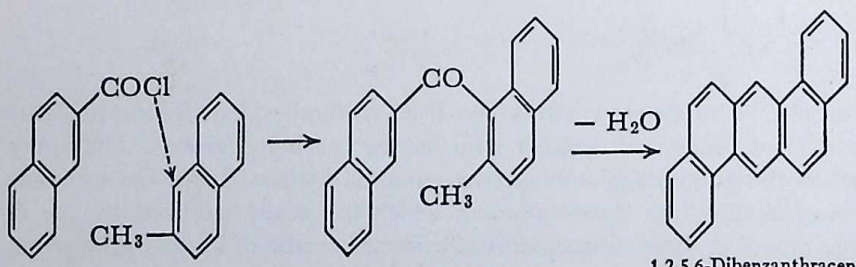


Pentacene



Hexacene

Carcinogenic Hydrocarbons. It has been known for many years that the workers in coal-tar refineries were susceptible to a skin cancer which came to be known as *tar cancer*. A series of systematic investigations on coal tar revealed that certain aromatic, condensed, polynuclear hydrocarbons are responsible for this disease. One of the most active **carcinogenic** (cancer producing) compounds is 1,2,5,6-dibenzanthracene. It can be synthesized by a Friedel-Crafts reaction between β-naphthoyl chloride and β-methylnaphthalene, followed by the application of the Elbs reaction, p. 555.



β-Naphthoyl chloride

1,2,5,6-Dibenzanthracene

An inspection of the structure of 1,2,5,6-dibenzanthracene shows it is related to both anthracene and phenanthrene.

Polynuclear Aromatic Compounds in Nature. Although the chief interest and importance of naphthalene and anthracene derivatives centers around the coal-tar dye industry, it would be a great mistake to believe that coal tar is the only source of these substances. Naphthalene, anthracene, and phenanthrene derivatives (or substances closely allied to them, as for example the corresponding quinones) have been found in the vegetable kingdom. Such substances, however, appear to occur less commonly than do the benzene

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derivatives, though this may be in part only a reflection of the greater difficulty of isolating them from the complex mixtures found in nature.

No simple naphthalene derivatives (such as the naphthols, for example) have been found in nature. Trihydroxynaphthalenes and derivatives of alpha naphthoquinone occur in certain very restricted classes of plants.

Derivatives of anthraquinone are quite widely distributed, though their occurrence is certainly much more specialized and localized than is the case of benzene derivatives. Alizarin and certain other hydroxy anthraquinones used as dyes have been mentioned. Hydroxyl derivatives of a methylanthraquinone occur as glucosides in a number of plants. Plant extracts containing such materials are known under the general name of *emodine*, and are used as drugs chiefly because of their laxative and purgative action. **Chrysophanic acid,** 1,8-dihydroxy-3-methyl-9,10-anthraquinone, may be cited as an illustration of the substances occurring in such drugs.

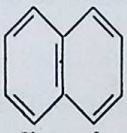
We shall see in Chap. 30 that a large group of substances which occur in nature contains the *hydrogenated* phenanthrene nucleus.

QUESTIONS AND PROBLEMS

1. Outline the steps in the isolation of naphthalene from coal tar.

2. Write structural formulas for 9,10-phenanthraquinone, naphthalic acid, 9,10-anthrahydroquinone, 4,4′-diaminobiphenyl, alizarin, naphthionic acid, 1-nitro-4-bromoanthracene, and 2-hydroxynaphthalene-3-carboxylic acid.

3. What are the reasons for preferring the following formula



for naphthalene, to a simple outline formula?

4. Outline the steps in the synthesis of 2-methylanthraquinone from coal-tar crudes.

5. Compare the addition reactions of benzene and naphthalene. Can you account for the differences noted?

6. Write structural formulas for the three naphthoquinones. Show the structural similarities between Vitamin K and α-naphthoquinone.

7. State the rules describing the position taken by substituents in naphthalene and in monosubstituted naphthalene derivatives.

8. Discuss briefly the chemistry of the anthraquinone vat dyes and their method of application to fabrics.

9. Outline the steps in the preparation of β-naphthol and β-naphthylamine from naphthalene.

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10. Write balanced equations for the following reactions: (*a*) anthraquinone and sodium hydrosulfite, (*b*) xylenol-1,2,4 and benzenediazonium chloride, (*c*) acenaphthene and chromic acid.

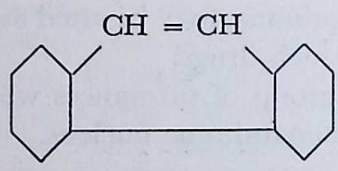
11. Write the structural formula for a typical anthraquinone mordant dye and explain how the dye is applied to a fabric.

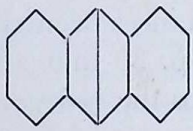
12. Write formulas for the resonating structures of naphthalene and biphenyl. Which group would you expect to have the greater effect on the dissociation of hexaaryl ethanes?

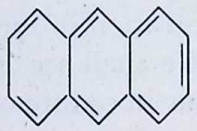
13. Compare and contrast the chemical properties of naphthalene, phenanthrene, anthracene, and tetraphenylethylene with special reference to their behavior with reagents which add to aliphatic derivatives of ethylene.

14. What is the Elbs reaction? Give at least one illustration. How do you think you might employ it in the synthesis of chrysene?

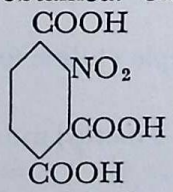
15. What facts would make you reluctant to write any of the following formulas for anthracene?







16. Which of the following substances do you think would couple with a diazonium salt under the usual conditions: (*a*) 9-hydroxyanthracene, (*b*) 9,10-anthrahydroquinone, (*c*) 2-hydroxyanthracene, (*d*) 9-methyl-10-hydroxyphenanthrene, (*e*) 1,8-dibromo-2,7-dihydroxynaphthalene, (*f*) *p*-hydroxybiphenyl, (*g*) picene, (*h*) R salt, (*i*) naphthalic acid, (*j*) chrysophanic acid.

17. When 2-methylnaphthalene is nitrated, two isomeric mononitro compounds are obtained. One of these on oxidation yields a compound of the structure 

, while the other gives 3-nitrophthalic acid. Write the structures of the isomeric nitro compounds formed by the nitration reaction.

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Chapter 29

ALICYCLIC COMPOUNDS

Having considered some representative aromatic hydrocarbons and their derivatives, we shall devote a chapter to the saturated and unsaturated alicyclic compounds. These substances are of interest because of the unusual reactivity of the smaller rings, because of a type of stereochemical isomerism which occurs in ring compounds, and finally because of the large number of natural products which contain alicyclic rings. A few of the more interesting of these natural products will be considered in the next chapter.

The Cycloparaffins and Their Derivatives. The simplest alicyclic compounds are the cycloparaffins which have already been mentioned in connection with petroleum (p. 105). These substances are isomeric with the ethylenic hydrocarbons and have the general formula C_nH_{2n}. Two hydrogen atoms are missing as compared with the corresponding paraffin hydrocarbon, C_nH_{2n+2}; these may be considered as having been removed in the formation of the ring. The table which follows gives the names and physical properties of some of the simpler cycloparaffins.

PHYSICAL PROPERTIES OF SOME SIMPLE CYCLOPARAFFINS

Name	*Formula*	*Freezing Point*	*Boiling Point*
Cyclopropane	$(CH_2)_3$	−126.6°	−34°
Cyclobutane	$(CH_2)_4$	−80°	−15°
Cyclopentane	$(CH_2)_5$	below −80°	49°
Cyclohexane	$(CH_2)_6$	6.5°	81°
Cycloheptane	$(CH_2)_7$	−12°	119°

General Characteristics of Alicyclic Compounds. With the exception of cyclopropane (the first member of the series), the characteristic reactions of the alicyclic compounds are very close to those

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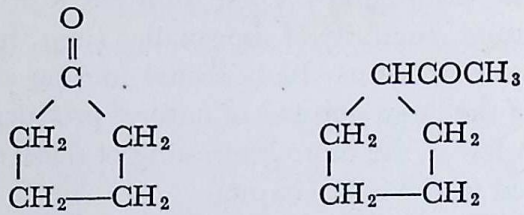
of the aliphatic; to a large extent we can transfer our knowledge gained in the one field to the other. We shall consider some peculiarities of cyclopropane compounds shortly, but shall first turn to the more general behavior of the other cycloparaffins and their derivatives. Just as we have alcohols, ketones, etc., which are derived from the paraffin hydrocarbons, so we have similar groups of alicyclic compounds. It should be recognized that functional groups which involve one or two valences can either be part of a ring or attached to a ring; thus we may have cyclopentanone and methyl cyclopentyl ketone. Functional groups, like carboxyl, which involve more than two valences naturally cannot be part of a ring.



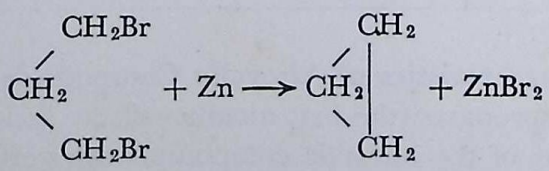
The various functional groups show the same reactions in the cycloparaffins as in the paraffins; the reactivity of the functional group is somewhat greater in the cycloparaffins, however. Cyclohexanone, for example, reacts more rapidly than diethyl ketone with such typical carbonyl reagents as bisulfite, hydroxylamine, and phenylhydrazine.

Methods of Closing an Alicyclic Ring. The reactions used to form alicyclic rings are, with one exception, the same reactions we have used to form carbon-carbon bonds in open-chain compounds. When these reactions take place, involving not two functional groups in two different molecules but two functional groups in the same molecule, the result is the closure of an alicyclic ring. The following reactions will serve as illustrations.

When an alkyl halide is treated with a metal a new carbon-carbon bond is formed and a paraffin hydrocarbon is obtained; this is the Wurtz reaction, page 41.

$$CH_3CH_2Br + 2Na + CH_3CH_2Br \longrightarrow CH_3CH_2CH_2CH_3 + 2NaBr$$

If a dihalide is used instead of a monohalide, the product is a cycloparaffin.



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The method is useful for preparing cycloparaffins containing less than seven carbon atoms in the ring.

Heating the calcium salts of the monobasic acids, or passing the vapors of these acids over a metallic oxide catalyst, furnishes ketones (p. 127).

$$2CH_3COOH \xrightarrow{MnO} CH_3COCH_3 + H_2O + CO_2$$

With dibasic acids, the two carboxyl groups already being in the same molecule, the reaction leads to cyclic ketones.

$$\begin{array}{l} CH_2CH_2COO \\ | \qquad\qquad \rangle Ca \\ CH_2CH_2COO \end{array} \longrightarrow \begin{array}{l} CH_2CH_2 \\ | \qquad\qquad \rangle CO + CaCO_3 \\ CH_2CH_2 \end{array}$$

By varying the metal used, this reaction can be made to serve as a useful synthesis of the alicyclic ketones containing from five to thirty-four carbon atoms in the ring.

A third method of preparing the alicyclic compounds makes use of a reaction which was discussed in connection with malonic ester. It will be recalled that by the interaction of iodine and the sodium derivative of malonic ester two malonic ester residues may be united (p. 276). If now the two malonic ester residues are a part of the same carbon chain, the result of the application of such a method will be the formation of an alicyclic ring.

$$\begin{array}{l} CH_2CH(COOC_2H_5)_2 \\ | \\ CH_2CH(COOC_2H_5)_2 \end{array} + 2NaOCH_3 \longrightarrow \begin{array}{l} CH_2CNa(COOC_2H_5)_2 \\ | \\ CH_2CNa(COOC_2H_5)_2 \end{array} + 2CH_3OH$$

$$\begin{array}{l} CH_2CNa(COOC_2H_5)_2 \\ | \\ CH_2CNa(COOC_2H_5)_2 \end{array} + I_2 \longrightarrow \begin{array}{l} CH_2-C(COOC_2H_5)_2 \\ | \qquad | \\ CH_2-C(COOC_2H_5)_2 \end{array} + 2NaI$$

In the above equations, the formulas of the disodium derivative have been written with the sodium atoms attached to carbon atoms merely for convenience of representation; see page 275.

In the presence of an alkali metal two molecules of a nitrile, RCH_2CN, interact in the following way:

$$RCH_2CN + RCH_2CN \xrightarrow{Na} \begin{array}{l} RCHCN \\ | \\ RCH_2C = NH \end{array}$$

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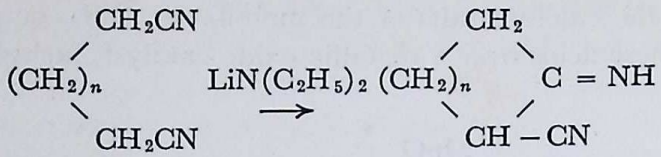
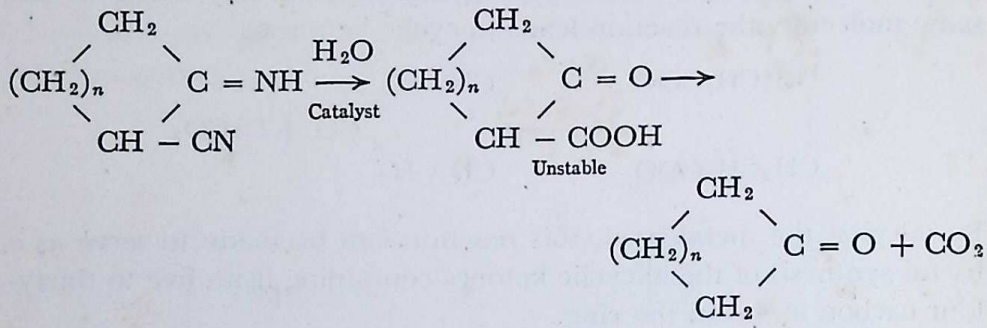
The same reaction applied to dinitriles is a valuable method of preparing cyclic ketones with large rings.

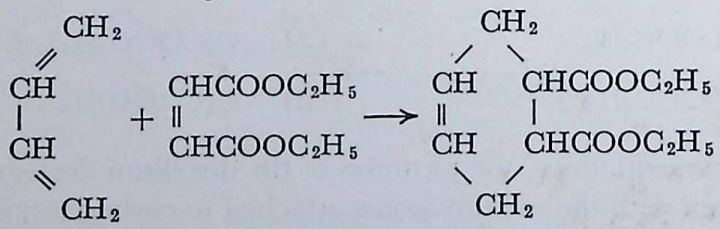


This product on hydrolysis yields a beta ketonic acid which, like acetoacetic acid, easily loses carbon dioxide, giving the cyclic ketone.



In order to prevent the interaction of *two* molecules with each other and to favor *internal* reactions between the two nitrile groups of one molecule, the concentration of the dinitrile is kept very low (i.e., the reaction mixture is kept very dilute). Under these conditions very good yields of the cyclic compounds may be obtained.

The exception referred to in the first paragraph of this section is the **diene synthesis.** This reaction *always* furnishes cyclic products. It can be used for preparing polycyclic systems, but in its simplest form it leads to six-membered alicyclic substances containing one double bond in the ring.



Equilibria and Rates in Ring Closure. We have already pointed out that, with the exception of the diene synthesis, the reactions which lead to the formation of alicyclic compounds are reactions between two atoms or functional groups in a single molecule. In addition, however, a reaction between the functional groups in two different molecules is also a possibility. Thus two molecules of a dinitrile can react with each other.

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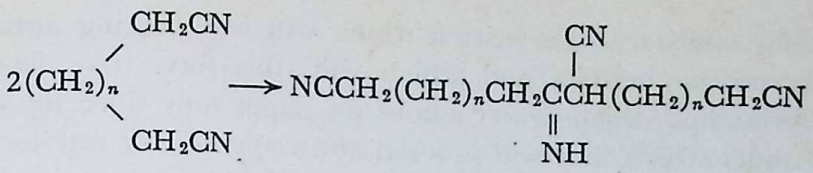
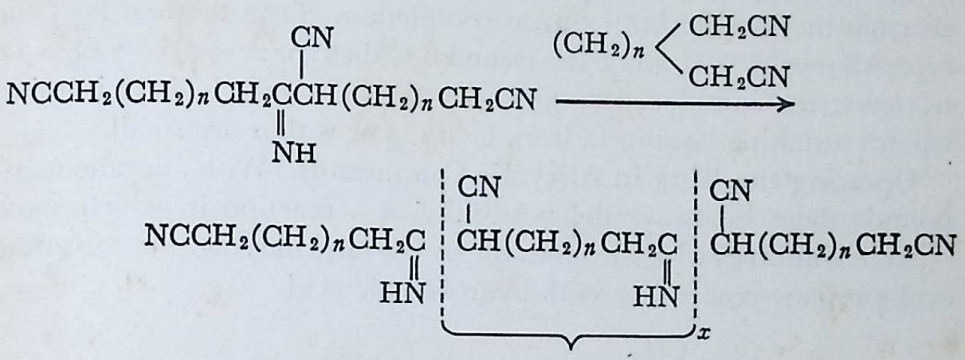


The product of this reaction still contains the two functional groups present in the original dinitrile, so that it can react further with more of the dinitrile and form eventually a product of high molecular weight.



In practice there is almost always a competition between the two processes: the one leading to cyclic compounds, the other leading to long open-chain molecules of high molecular weight. (This was very strikingly shown in the formation of anhydrides from the dibasic acids.) The *rate* of the *intermolecular* reaction may be decreased by operating in dilute solution where there is less chance of collision between the functional groups of two different molecules. It seems most likely that the factor governing the rate of these reactions is the frequency of collisions between functional groups. When the two groups can approach each other fairly frequently as a result of the twisting of the chain due to thermal agitation of the molecules in an open-chain compound, the chances of ring closure are increased. Construction of the models of the compounds $X(CH_2)_nY$, where n = 3,4,5,6,7, etc., will show that the chances of X and Y approaching each other decrease rapidly as n increases. Therefore we find as a general rule high rates of ring closure only when rings containing less than seven atoms are formed. Not only the size of the ring, but the number, nature, and location of the substituents on the carbon atoms of the chain have a profound influence on the rate of the ring closure. These factors affect the energy relations and hence the equilibrium relatively little, however. Consequently there are many

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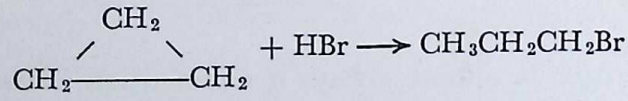
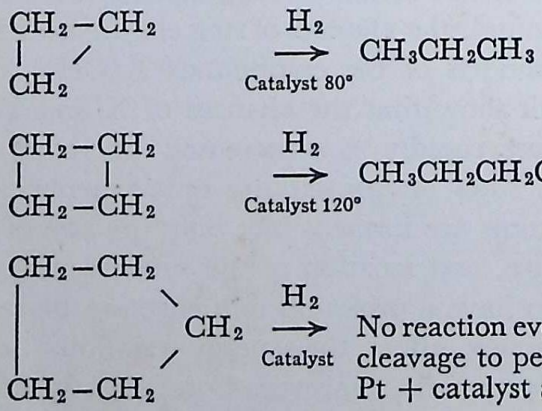
reactions which can be written which will lead to ring formation, which are exothermic, and which will, therefore, have favorable equilibria; but which are reactions on paper only since the conditions under which they will proceed at an appreciable rate have not been found. Usually the competing reaction involving many molecules takes place more rapidly. In general the energy relations in reactions of the type $X(CH_2)_nY \longrightarrow (CH_2)_n + XY$, are not very different from comparable reactions of the type $CH_3(CH_2)_mX + CH_3(CH_2)_pY \longrightarrow CH_3(CH_2)_{m+p}CH_3 + XY$. Where both reactions are strongly exothermic they would both run to completion. Since the first is of the type $AB \longrightarrow A + B$, while the second is of the type $A + B \longrightarrow C + D$, however, the considerations given on page 170 must be kept in mind when estimating equilibria from heat changes that are small.

Opening the Ring in Alicyclic Compounds. With alicyclic compounds there is always the possibility of a reaction in which some reagent combines with the molecule by opening the ring. For example, cyclopropane reacts thus with hydrobromic acid.



The individual compounds differ enormously in the rate at which such reactions proceed and the conditions which are necessary in order to bring them about. Many cyclopropane compounds are extremely reactive and the ring opens easily. Other cyclic compounds with larger rings rarely enter into such reactions. For example, cyclopropane is hydrogenated to propane by hydrogen and a catalyst at 80°, while cyclobutane with the same catalyst requires a temperature of 120°. *Larger rings in alicyclic hydrocarbons are not opened by hydrogenation under usual conditions* (below 200°).



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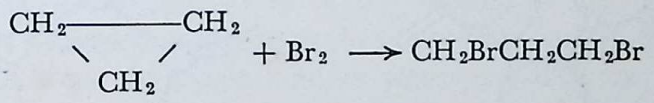
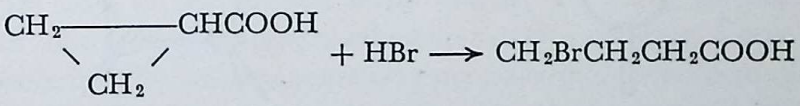
These striking differences are the result of differences in the rate of reaction and not of differences in equilibrium constants. The inability to open carbocyclic rings by hydrogenation at moderate temperatures is exactly like the failure to cleave paraffin hydrocarbons with hydrogen and a catalyst. Certain three- and four-membered rings are exceptional in that they are opened readily. Why these substances react so rapidly with hydrogen and a catalyst, and also often with bromine and with the halogen acids, is not clear. The hydrogenation of cyclopropane is more exothermic than the hydrogenation of cyclopentane (about 25 kg-cal as compared with about 14 kg-cal). This is not the basic reason for the difference in behavior given above, however, for the equilibrium constants in the hydrogenation of all the cycloparaffins correspond to essentially complete hydrogenation.

Cyclopropane (Trimethylene). Cyclopropane is made from trimethylene bromide and sodium or zinc. It has excellent anesthetic properties, but its high cost of production prevents its wider use in surgery.

In cyclopropane itself and many of its derivatives, the ring is opened even when the compounds are treated with such reagents as bromine and hydrobromic acid at room temperature.



$$\begin{array}{c} CH_2 \text{———} CH_2 \\ \diagdown \quad \diagup \\ CH_2 \end{array} + Br_2 \longrightarrow CH_2BrCH_2CH_2Br$$



$$\begin{array}{c} CH_2 \text{———} CHCOOH \\ \diagdown \quad \diagup \\ CH_2 \end{array} + HBr \longrightarrow CH_2BrCH_2CH_2COOH$$

Such cleavages of alicyclic rings also occur with cyclobutane and its derivatives, but not with the larger rings unless groups are present which cause the cleavage of even open-chain compounds.

Baeyer's Strain Theory. Somewhat more than fifty years ago, chemists were much impressed by the number of derivatives of cyclopentane and cyclohexane which were found in nature and which were readily prepared in the laboratory. They were also impressed by the ease with which five- and six-membered heterocyclic rings were formed. We have encountered a number of such instances in previous chapters; for example, only gamma and delta hydroxy acids readily form lactones (p. 240); only those dibasic acids whose cyclic anhydrides contain five- or six-membered rings form these anhydrides directly (p. 226).

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As an explanation of all these facts, Baeyer[1] in 1885 suggested his strain theory. He started with the regular tetrahedral carbon atom which had already provided an adequate explanation of stereoisomerism. In this atom the four valence forces are directed from the center to the corners of a regular tetrahedron, and therefore form an angle of 109° 28′ with each other (Fig. 18). In the union of two atoms, Baeyer assumed that these valence forces must lie joined in a straight line between the centers of the atom. If this assumption is correct, it is easy to see that a three-membered carbon ring can only be formed by a distortion of the valence angles of the carbon atoms. This is illustrated by the diagram shown in Fig. 19. The distortion or displacement of the valence angle can be calculated by simple geometry as 24° 44′; in the cyclobutane ring, the distortion is less (9° 44′), and in a cyclopentane ring, the distortion is less than a degree (44′).

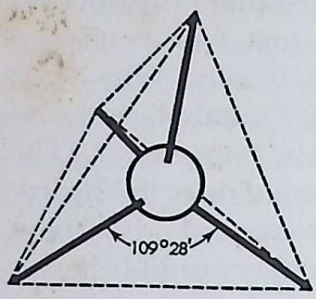

FIG. 18. Diagram showing normal valence angles of a carbon atom.

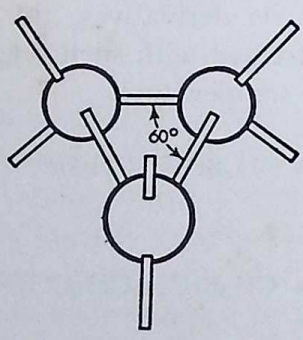

FIG. 19. Drawing of a model representing a cyclopropane ring.

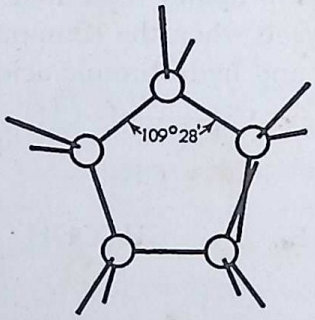

FIG. 20. Diagram showing the close approach of the terminal atoms of normal pentane when all the carbon atoms lie in a plane.

The cyclopentane ring can thus be closed without appreciable distortion; this is shown in the diagram (Fig. 20) of a model of a five-membered chain *so manipulated as to bring the terminal atoms as near together as possible.* It is clear that the ends of a five-carbon chain can approach very close to each other without any distortion of the valence bonds; this, of course, is not so with a four- or three-membered chain. Baeyer supposed that the distortion of the valence-angles in the three-

[1] Adolph von Baeyer (1845–1917). Professor of Chemistry at the University of Munich for more than forty years.

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or four-membered rings caused a *strain* in the molecule and that this strain was responsible for the fact that many of these compounds combined with various reagents: in so doing the ring is opened and the strain is relieved. No better explanation has yet been given.

Baeyer also assumed that all the atoms in a ring are in the same plane: in this assumption he was in error. In rings larger than six carbon atoms this would require expansion of the valence angles, and, in very large rings it would result in almost incredible strain. We know now that saturated rings containing more than five atoms are not planar. This is shown for cylohexane in Fig. 21.

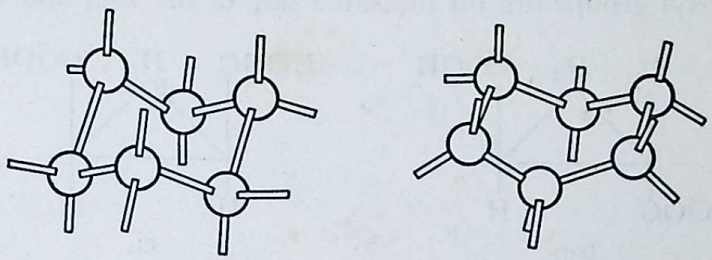
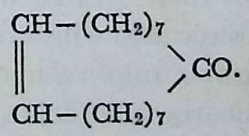


FIG. 21. Drawing of models representing two phases of a strainless cyclohexane ring. (The two phases are readily interconvertible by oscillation of the atoms and, therefore, do not represent isomeric forms.)

Many Membered Rings. A development of recent years has been the preparation and the study of the properties and reactions of alicyclic compounds containing up to thirty-four carbon atoms in the ring. In this work the cyclic ketones were prepared by heating the thorium salts of the dibasic acids and by the condensation of dinitriles, both reactions described earlier in this chapter. These many-membered cyclic ketones show no essential differences from aliphatic compounds. From the ketones by reduction, the corresponding secondary alcohols and finally the cyclic hydrocarbons may be prepared. In this way, for example, cyclotriacontane, $C_{30}H_{60}$, a solid melting at 56°, may be prepared from the corresponding cyclic ketone.

When the compounds with large rings are once formed, they are perfectly stable, and the ring cannot be opened any more readily than an open chain can be cleaved.

A very interesting cyclic ketone with a seventeen-membered ring occurs in nature as the chief constituent of the natural, odoriferous material known as *civet*. This ketone is known as *civetone*, and has been proved to have the following formula:



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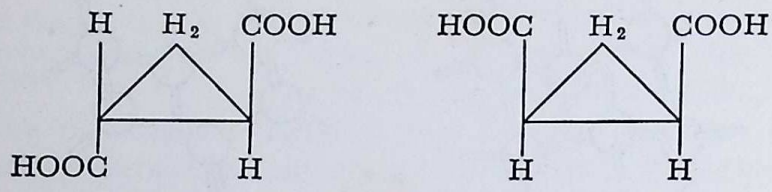
The isolation of this ketone and the proof of its structure by Ruzicka led this same investigator to attempt the preparation of cyclic ketones with large rings. The striking results of this study have just been discussed.

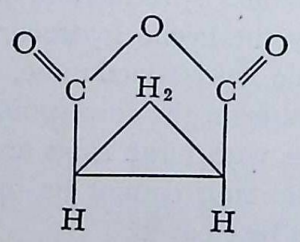
Stereochemistry of Cyclic Compounds. If a cyclic compound is asymmetrical, it can exist in two mirror images which correspond to two optical isomers, a dextro and a laevo form. Many such cyclic compounds have been resolved. If we construct a model of cyclopropane in which we substitute two hydrogens by two carboxyl groups it is easy to see that we will have one compound in which the two carboxyl groups are on the same side of the ring and a second



Trans Cis

compound in which they are on opposite sides. These two formulas represent two different compounds and, following the nomenclature used with geometrical isomers (p. 316), they are called *cis* and *trans isomers*. It should be noted that in the formulas printed above the carbon atoms of the ring are omitted; this is frequently done in writing the formulas of cyclic compounds.

One of these acids, like maleic acid, easily loses water on heating and forms an anhydride. In this anhydride there are two rings joined together, a carbon ring and a carbon-oxygen ring.



Anhydride of cis form

The other acid, the trans acid which does not form an anhydride, is asymmetrical. It should, therefore, be resolvable. This we find to be so: the cyclopropane dibasic acid which does not form an anhydride is a racemic mixture separable into a *d* and *l* form.

Two cyclohexane-1,2-dicarboxylic acids, which correspond to the

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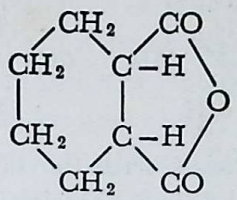
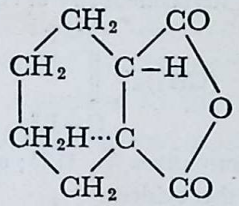
cis and trans cyclopropane dicarboxylic acids, are known. *Both* cyclohexane dicarboxylic acids lose water to form anhydrides.



Anhydride of cis-cyclohexane dicarboxylic acid.
Both hydrogen atoms attached to the middle carbon atoms lie on the same side of the double ring system.



Anhydride of trans-cyclohexane dicarboxylic acid.
The two hydrogen atoms attached to the middle carbon atoms extend on different sides. One lies above, the other (shown with a dotted line) lies below a plane passing through the general direction of the exterior of the two rings.

The difference in behavior between cyclopropane and cyclohexane in this regard is due to the fact that the cyclopropane ring must by necessity have the three carbon atoms in a plane, and is rigid. In the cyclohexane ring we are dealing with a more flexible system. The carbon atoms do not lie in one plane, and therefore the two carboxyl groups may be near enough to each other in space in both the cis and trans compounds so that in either case a new ring may be formed by loss of water. This can only be made evident by a study of the models themselves, and the student who is interested is advised to construct such models. The existence of anhydrides of both cis and trans cyclohexane-1,2-dicarboxylic acid, $C_6H_{10}(COOH)_2$, is conclusive evidence that the atoms of the cyclohexane ring do not lie in a plane.

Inositol illustrates the fact that it is possible to have asymmetry and optical isomerism in compounds which contain no asymmetric atom. Inositol, hexahydroxy-cyclohexane, can exist in eight isomeric forms which differ in the arrangement of hydroxyl groups and hydrogen atoms above and below the plane of the ring. Seven of these isomers possess some symmetry, but the eighth is asymmetric and has been resolved into its *d* and *l* forms.

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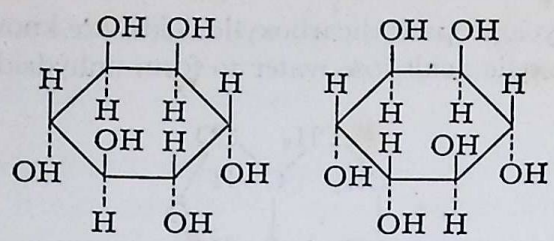
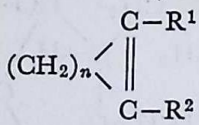


A comparable situation exists with the hexachlorocyclohexanes, the substances obtained by adding chlorine to benzene. One of the isomers, known as 666 from its empirical formula, $C_6H_6Cl_6$, is an insecticide comparable in effectiveness with DDT (p. 528).

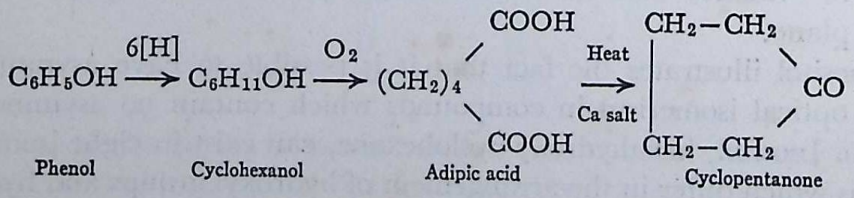
It is worthy of note that the stereochemistry of compounds of the type



is similar to that of acetylene derivatives (p. 317); only one form is possible. A construction of a model will make this evident.

Alicyclic Compounds from Aromatic Compounds. In recent years, the catalytic hydrogenation of aromatic compounds under pressure at elevated temperatures has made possible the industrial preparation of certain alicyclic compounds. For example, cyclohexane, C_6H_{12} (also known as *hexahydrobenzene*), may be thus prepared from benzene, C_6H_6, and cyclohexanol, $C_6H_{11}OH$, from phenol, C_6H_5OH. Such methods often provide the most convenient way of preparing alicyclic compounds, if the corresponding aromatic compound is readily available.

The vigorous oxidation of alicyclic alcohols, ketones, or unsaturated compounds, results in the opening of the ring. This occurs in rings of any size just as similar reactions cause the cleavage of open chains. The oxidation of cyclohexanol provides a relatively cheap method of preparing adipic acid. From this, in turn, cyclopentanone may be prepared. Thus, it is possible to synthesize even a five-membered ring compound from phenol by the following series of reactions.



Hydrogenated, Polycyclic, Aromatic Compounds. Naphthalene and its derivatives may be hydrogenated by means of hydrogen gas and a suitable catalyst. The completely hydrogenated compounds

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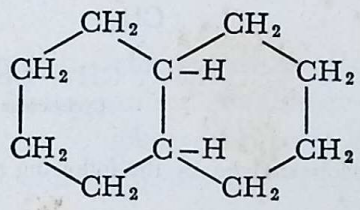
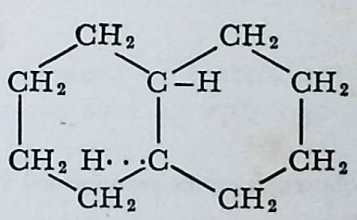
contain ten more hydrogen atoms than the parent substances and are known as *decalins* (decahydronaphthalenes). Since a completely hydrogenated aromatic compound is also sometimes called a *perhydro compound*, decalin, $C_{10}H_{18}$, might be named *perhydronaphthalene*. Completely hydrogenated phenanthrene, $C_{14}H_{24}$, called *perhydrophenanthrene*, is the skeleton of a large and varied group of natural products of great biochemical importance (Chap. 30).

Decalin can exist in two stereochemically isomeric forms. They are very similar to the anhydrides of the two cyclohexane dicarboxylic acids except that the second ring is a carbon ring and not an oxygen-containing anhydride ring. The construction of models with strainless rings will help in understanding this type of stereoisomerism. On paper the two isomers may be represented by using the convention that the hydrogen atoms attached to the middle carbon atoms are written with a heavy line if they extend above the paper and a dotted line if below.

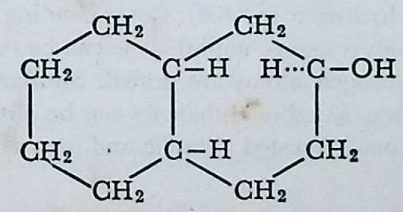


Cis decalin
(bp 193°)

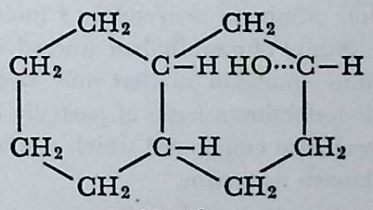


Trans decalin
(bp 185°)

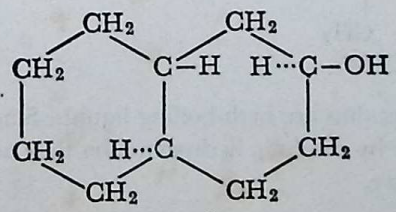
When one of the CH_2 groups in decalin carries a substituent, four stereoisomers are possible. All four isomers of perhydro β-naphthol (2-decalol) have been isolated. Using the same conventions in regard to the representation of three-dimensional formulas on paper, we may write their formulas as follows:



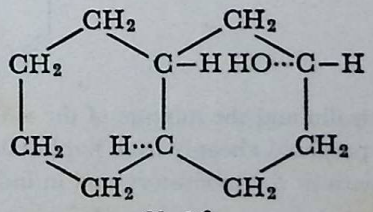
Mp 105°



Mp 17°



Mp 75°



Mp 53°

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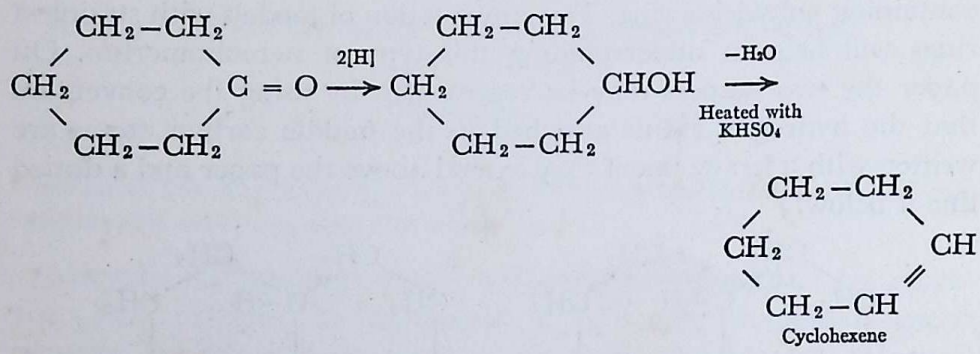
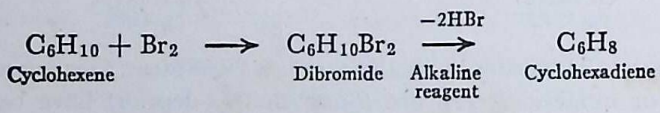
The first pair of isomers may be considered as derived from cis decalin; the other pair from trans decalin. This type of isomerism is very common among complex alicyclic compounds.

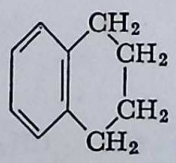
Unsaturated, Alicyclic Compounds. The preparation of unsaturated alicyclic compounds follows the general methods used with open-chain compounds. For example, we may prepare a six-membered ring containing one double bond by the following series of reactions. The resulting compound is called *cyclohexene*, the nomenclature following that of the open-chain compounds, except that the prefix "cyclo" is added.



Cyclohexene may be transformed into cyclohexadiene by the following series of reactions.



The hydrogenation of benzene cannot be controlled so that such intermediate products as cyclohexadiene or cyclohexene may be isolated. The reason for this lies in the low affinity of benzene for 1 mole of hydrogen (p. 406). Corresponding to the greater affinity of naphthalene toward various reagents, naphthalene can be reduced by sodium amalgam so that only two hydrogen atoms are added. Similarly, by catalytic reduction a series of partially hydrogenated naphthalenes can be obtained. The tetrahydro compound which contains one saturated alicyclic and one aromatic ring is known as *tetralin*.



Both tetralin and the mixture of the two decalins are high-boiling liquids. Since they can be prepared cheaply from naphthalene by catalytic hydrogenation they are used often, both in the laboratory and in industry.

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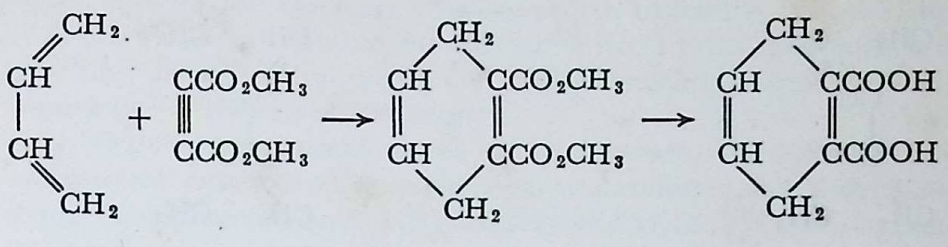
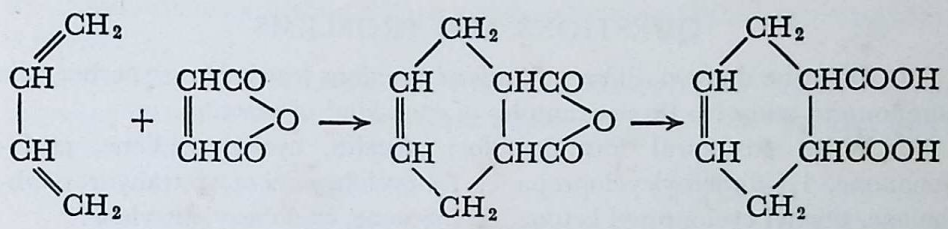
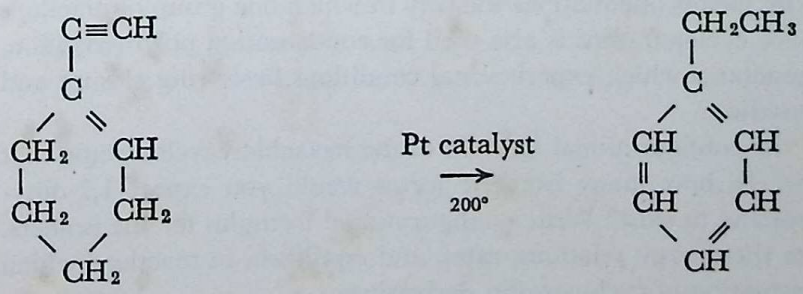
Unsaturated alicyclic compounds, as was pointed out earlier, result directly from the diene synthesis. Thus, butadiene and acetylene dicarboxylic ester furnish a cyclohexadiene derivative, while butadiene and maleic anhydride furnish a cyclohexene derivative.





Aromatic Compounds by Rearrangement of Unsaturated Alicyclic Compounds. A number of unsaturated alicyclic compounds are known which are isomeric with the aromatic compounds. Some of them can be prepared synthetically; a few occur in nature. Because of the high resonance energy of the aromatic ring as compared with any other arrangement of double linkages, the formation of the aromatic compound by rearrangement of the alicyclic isomer is a strongly exothermic reaction. The equilibrium constant is correspondingly in favor of the rearranged product. Though the heat evolved in the reaction may be large (about 30 kg-cal), the unsaturated alicyclic isomer does not rearrange spontaneously. On the contrary the shift of double linkages and hydrogen atoms occurs only under the influence of a catalyst. Two examples of such rearrangements follow by way of illustration.



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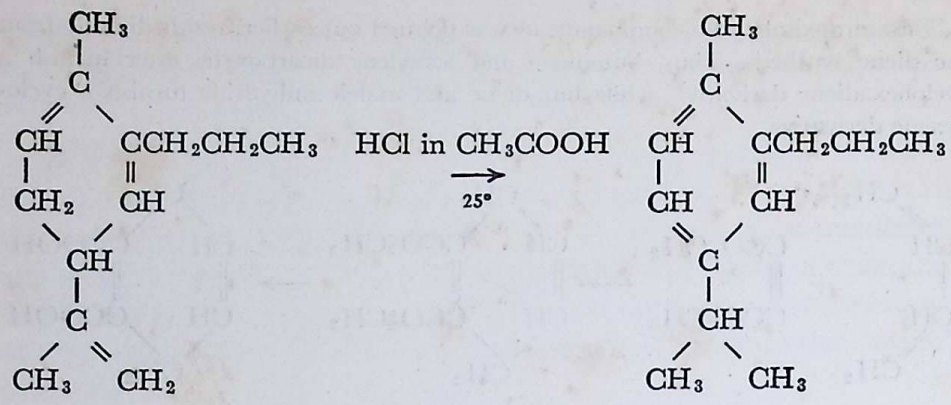
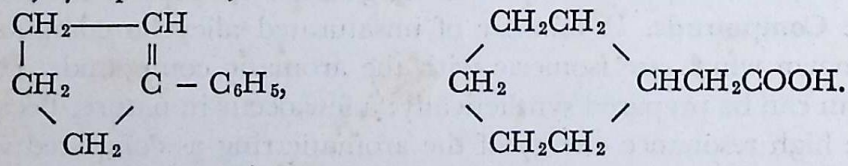


QUESTIONS AND PROBLEMS

1. Describe the two different kinds of reactions which furnish carbocyclic compounds, and give three examples of each kind of reaction.

2. Write structural formulas for: decalin, cyclopentadiene, cyclononanone, 1,1-dimethylcyclopropane, 1,4-cyclohexadiene, tetrahydronaphthalene, phenyl cyclopropyl ketone, cyclobutene, cyclohexylacetylene.

3. Outline the steps in the synthesis from phenol or benzene of: cyclohexene, cyclopentanol,



4. If 2-methylnaphthalene is hydrogenated to the perhydro compound, how many stereoisomers would you expect to obtain? How could these compounds be converted back to methylnaphthalene? How many stereoisomeric perhydrophenanthrenes are theoretically possible?

5. Outline two different methods of preparing cyclooctane from trimethylene glycol.

6. Isophthalic acid (benzene-1,3-dicarboxylic acid) does not form a cyclic anhydride. The hexahydro compound formed from it by catalytic hydrogenation does form a cyclic anhydride when treated with dehydrating agents. Explain.

7. Show by means of equations the way in which one group of reactions used to prepare cycloparaffins is also used for condensation polymerization. With given reactants which experimental conditions favor ring closure and which condensation?

8. Write the configurational formula of the hexachlorocyclohexane that is asymmetric. In how many isomeric forms would you expect 1,2-dihydroxycyclopropane to exist? Write configurational formulas for the isomers.

9. Discuss the energy relations, rates, and equilibria in reactions which lead to the formation of cycloparaffin derivatives.

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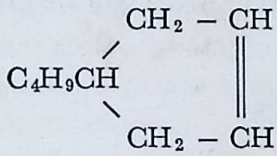
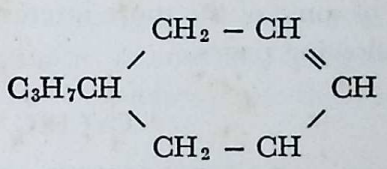
10. Predict what reactions (if any) would occur when the following compounds are treated with concentrated hydrobromic acid: cyclopropane, cycloheptanol, cyclooctene, cyclodecane.

11. What is meant by the term *strainless ring?* What conclusions may be drawn from the fact that large ring compounds cannot be opened except by drastic treatment? How can one account for the fact that compounds with large rings are difficult to prepare by methods which give good results in forming five- and six-membered rings?

12. Cyclohexanone readily forms an oxime which, when treated with concentrated sulfuric acid or phosphorus pentachloride and then alkali, yields ε-aminocaproic acid, $NH_2CH_2CH_2CH_2CH_2CH_2COOH$. Indicate the transformations involved during these reactions. What rearrangement is involved?

13. A compound is known to be represented by either one of the two following formulas: by what reactions would you be able to establish which formula is correct?

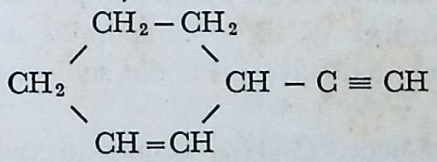




By what steps could you prepare the cyclopentene compound, starting with malonic ester?

14. A mixture of the four 2-decalols was oxidized with chromic acid to give the corresponding ketones. How many isomeric products would you expect?

15. What explanation can you offer for the fact that



in the presence of a suitable catalyst rearranges to ethylbenzene?

16. What reaction could you use to determine whether a compound C_6H_8 was cyclohexadiene-1,3 or cyclohexadiene-1,4?

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Chapter 30

NATURAL PRODUCTS CONTAINING ALICYCLIC RINGS: TERPENES, STEROLS, SEX HORMONES

A great variety of substances which possess alicyclic rings are found in nature. The simplest of these contain a six-membered ring and occur principally in plants. Others contain partially hydrogenated naphthalene rings, and several different classes of important compounds contain a reduced phenanthrene nucleus. A very brief summary of some of the more interesting representatives will be given in the following pages.

CYCLIC TERPENES

A group of unsaturated alicyclic compounds, known as the *cyclic terpenes* and having the formula $C_{10}H_{16}$, are found widely distributed in certain plants. They occur in essential oils, particularly those obtained from citrus fruits. They also occur in oil of turpentine and similar materials made from coniferous trees. Certain cyclic alcohols and ketones closely related to the cyclic terpenes are also found in the plant world. A number of these compounds are of considerable practical importance and have been the subject of a great deal of investigation.

Limonene. Limonene, $C_{10}H_{16}$, occurs in two optically active forms, a dextro compound which is present in many essential oils from citrus fruits, and a laevo limonene which can be obtained from the leaves of certain pines. The racemic compound, known as *dipentene*, can be prepared in the laboratory either by a complete synthesis or by a transformation of certain other terpenes. Dipentene is also formed along with other products by heating isoprene at 300°; in this reaction, which is a diene synthesis, two isoprene molecules combine with each other. These compounds are liquids (bp 177°). As the formula shows, they are derivatives of cyclohexene; one methyl group and an unsaturated side chain containing three carbon atoms are attached to the opposite extremities of the ring. The asymmetric

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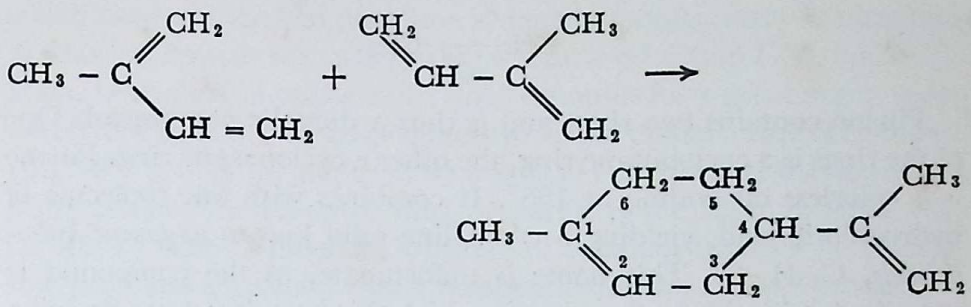
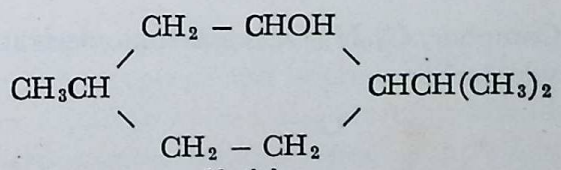
carbon atom is printed in heavy type. As would be expected, the two double bonds react with a variety of reagents.



Limonene (*d, l*-limonene-dipentene)

The nature of the carbon skeleton in limonene was first established by converting it into the aromatic hydrocarbon known as *para cymene* (p. 417). This was done by bromination and subsequent elimination of hydrobromic acid. The structure of cymene was readily established by the methods employed in aromatic chemistry. Subsequently, dipentene itself was synthesized from a cyclohexanone derivative of known structure.

Menthone and Menthol. Two oxygen-containing substances closely related to limonene occur in certain essential oils. One of these is a saturated alcohol, **menthol,** $C_{10}H_{20}O$, which is the chief constituent of peppermint oil. Associated with it is the corresponding ketone, **menthone,** $C_{10}H_{18}O$. Menthol is a solid melting at 43.5°, while menthone is a liquid boiling at 207°. Both of these substances have a strong peppermint odor and are laevorotatory. It will be noted that menthol is an hydroxyl derivative of the completely hydrogenated limonene molecule. The characteristic reactions of the hydroxyl group and the ketonic group are shown by menthol and menthone respectively.



Menthol

Pinene. Pinene, $C_{10}H_{16}$, is the principal constituent of turpentine oil. It occurs in two forms, the dextro in American turpentine and the laevo in European turpentine. **Turpentine** is manufactured from the sap of coniferous trees by a distillation process. It is widely used as a solvent in the paint industry.

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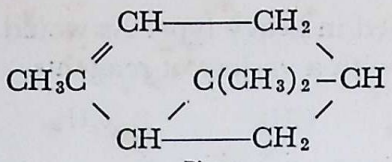
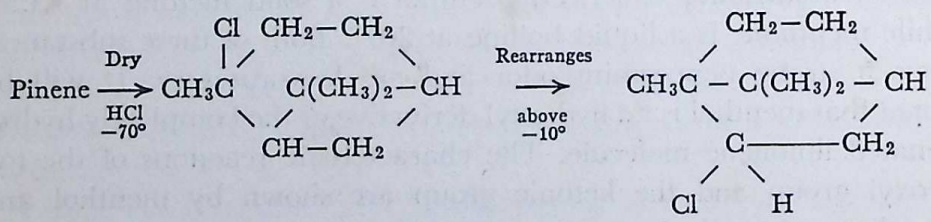


Pinene

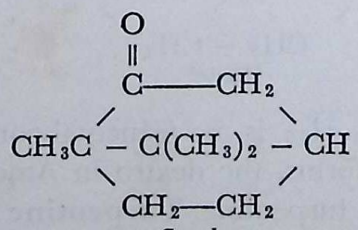
Pinene contains two rings and is thus a **dicyclic compound.** One of the rings is a cyclobutane ring, the other a cyclohexene ring. Pinene is a colorless oil boiling at 156°. It combines with one molecule of hydrochloric acid, yielding a crystalline solid known as *pinene hydrochloride*, $C_{10}H_{17}Cl$. This name is unfortunate, as the compound is not a hydrochloride in the sense in which this term is used to describe the salts of bases; it is really a chloro derivative of a saturated dicyclic compound. During the addition of hydrogen chloride a rearrangement of the cyclobutane ring to a cyclopentane ring occurs. This rearrangement was for a long time the cause of a great deal of confusion in regard to the structure of pinene and its derivatives. Pinene hydrochloride has a camphorlike odor and is known as artificial camphor. It is not to be confused, however, with true synthetic camphor.

At −70° pinene combines with dry hydrogen chloride without rearrangement. The halogen acid adds to the double linkage according to Markownikoff's rule. The tertiary halide thus formed rearranges at −10° or higher temperatures; in this process the bridge ring enlarges.



The final product "pinene hydrochloride" is properly called *bornyl chloride* (see p. 583).

Camphor. Camphor, $C_{10}H_{16}O$, is a ketonic derivative of a saturated dicyclic hydrocarbon.



Camphor

Camphor (often called *Japan camphor*) is obtained by the steam distil-

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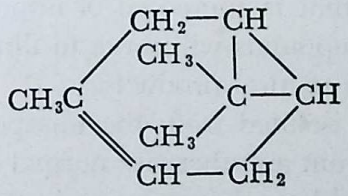
lation of the wood, twigs, and leaves of the camphor tree (*laurus camphora*). It is produced almost entirely in the Orient. The form which occurs in the camphor tree is dextrorotatory, and it is obtained as colorless crystals with a very characteristic odor (mp 175°, bp 204°). It has been used in medicine in small amounts for a great many years and is now used in very large quantities in the manufacture of celluloid (p. 298). It may be prepared by a series of chemical transformations from pinene; the material thus prepared is the racemic form (*d,l*, camphor). The commercial synthesis of camphor from oil of turpentine produces a product which competes with the natural product.

The alcohol which corresponds to camphor is **borneol,** $C_{10}H_{18}O$, mp 206°. It is found naturally in certain trees in the Orient. It can be prepared by the reduction of camphor. The chemical preparation of camphor from pinene involves the preparation of bornyl chloride, the hydrolysis of this to the racemic borneol, and subsequent oxidation to the ketone.

The similarity in the structural skeletons of limonene, pinene, and camphor becomes apparent when one realizes that the isopropenyl group $\left(-C\begin{matrix}\diagup\!\!\!\!\diagup CH_2\\ \diagdown CH_3\end{matrix}\right)$ attached only to carbon atom 4 in limonene, joins carbon atoms 4 and 6 in pinene, and joins carbon atoms 4 and 1 in camphor. The third possibility, in which the isopropenyl group joins carbon atoms 4 and 5 to form a cyclopropane ring, is realized in carene.



Carene

Relation of Terpenes to Isoprene. A very interesting relationship exists between cyclic terpenes and isoprene. This unsaturated hydrocarbon, $CH_2 = C(CH_3)CH = CH_2$, we have already encountered as being the fundamental building stone of the rubber molecule. If we examine the structure of the cyclic terpenes it will be seen that they all may be regarded as containing two isoprene nuclei joined together in different ways. This is illustrated below with the limonene and the pinene skeletons by printing the carbon atoms of one isoprene unit in heavy type. The reader can easily convince himself that a similar situation exists in regard to camphor. It will be clear that it is

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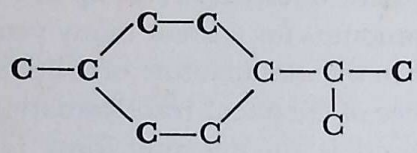
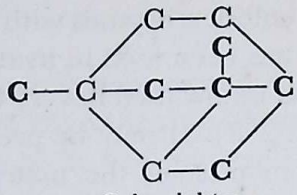
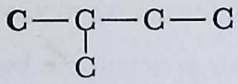
the occurrence of the carbon chain of isoprene which is of importance, and that different degrees of hydrogenation are obviously involved in the different terpene compounds.



Carbon skeleton of limonene and menthol



Carbon skeleton of pinene

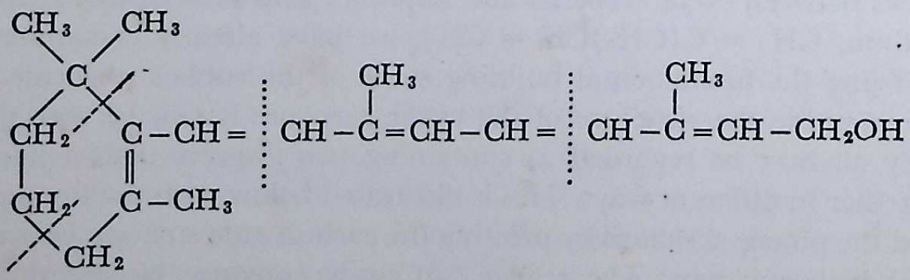


Carbon skeleton of isoprene

The terpenes themselves are often defined as naturally occurring substances of the formula $(C_5H_8)_n$, that is, multiples of the isoprene unit; those having the formula $C_{10}H_{16}$ are known as the *terpenes* proper and include both open-chain and alicyclic compounds. Higher terpenes are also known; those with the molecular formula $C_{15}H_{24}$, that is, $(C_5H_8)_3$, are called *sesquiterpenes*.

The Isoprene Rule. Vitamin A. The occurrence in natural products of structures which can be considered to be built up of isoprene units is so frequent that chemists making preliminary decisions between alternative formulas for a naturally occurring compound will choose the structure that is composed of isoprene units. Vitamin A and a few related compounds will serve to illustrate the importance of the isoprene unit in natural products.

Vitamin A can be isolated from the unsaponifiable residue from fish oils. Its absence from an otherwise normal diet leads to a state of ill-health characterized by a degeneration in the structure of the eye, a condition known as *xerophthalmia*. The structure of vitamin A is shown below, with dotted lines to indicate the isoprene residues.



Vitamin A can be replaced in the diet of animals by the carotenes,

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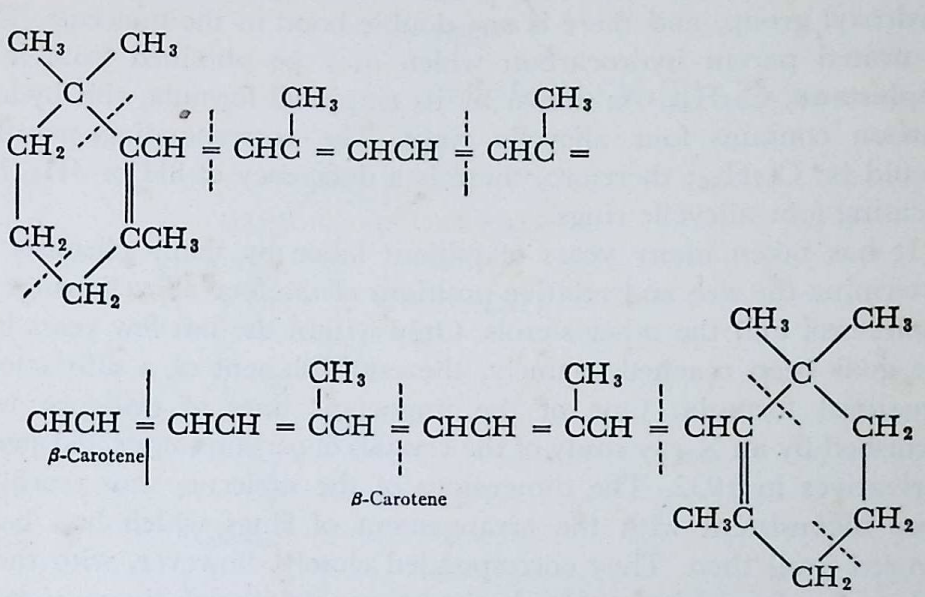
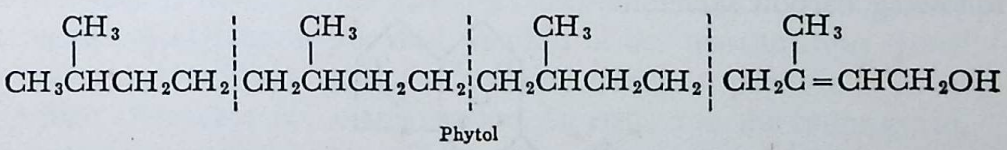
three isomeric compounds which are transformed into vitamin A in the liver and which are, therefore, provitamins. The structure of one of the isomers, **β-carotene,** is shown below. Again the isoprene units are obvious.



Finally, the occurrence of isoprene building units in an open-chain compound is shown by the formula of **phytol,** an alcohol obtained on hydrolysis of chlorophyll (p. 625).



STEROLS AND BILE ACIDS

The sterols are a group of complex alicyclic alcohols. They are colorless, crystalline solids, soluble in organic solvents, and usually found in the unsaponifiable portion of fats (p. 209). The commonest example is **cholesterol,** which occurs widely distributed in animals, particularly in relatively large quantities in the spinal cord and in human gallstones. The sterols which occur in plants are known as the **phytosterols;** there are a great many of these known. Esters of the sterols, as well as the free sterols, occur in plants and animals. **Lanolin,** or wool fat, is a very complicated mixture of sterols and sterol esters.

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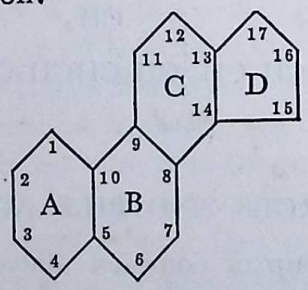
Cholesterol. Cholesterol is a colorless, crystalline solid which melts at 148° to 151°. Like all the sterols, it is difficult to purify when it is contaminated with similar substances. The molecular formula of cholesterol is $C_{27}H_{46}O$. The oxygen atom is present in a secondary hydroxyl group, and there is one double bond in the molecule. The saturated parent hydrocarbon which may be obtained from it is **cholestane,** $C_{27}H_{48}$. As shown by its empirical formula, this hydrocarbon contains four alicyclic rings. The corresponding paraffin would be $C_{27}H_{56}$; therefore, there is a deficiency of 8H or $4H_2$, indicating four alicyclic rings.

It has taken many years of patient labor by many chemists to determine the size and relative positions of the four alicyclic rings in cholesterol and the other sterols. Only within the last few years has the goal been reached, namely, the establishment of a satisfactory structural formula. One of the important lines of evidence was furnished by an X-ray study of the crystals of certain sterols and sterol derivatives in 1932. The dimensions of the molecule thus revealed were inconsistent with the arrangement of rings which had been favored until then. They corresponded closely, however, with those of a molecule which contained a hydrogenated phenanthrene ring to which an additional alicyclic ring had been fused. In the next few years it was clearly established that all the sterols and, as we shall see, many other classes of interesting compounds as well contain the following carbon skeleton:



This arrangement of carbon atoms corresponds to that of a hydrocarbon in which a phenanthrene nucleus (rings A, B, C) and a cyclopentane (ring D) have been fused together. Such a hydrocarbon, if the first three rings are aromatic and ring D a cyclopentene ring (CH_2 at 15,16,17, double bond at 13,14) is known as *cyclopentenophenanthrene.* Since in the sterols all the rings are alicyclic, they may be regarded as derivatives of the completely saturated compound, **perhydrocyclopentanophenanthrene.** This parent hydrocarbon can also be considered as consisting of a perhydrophenanthrene ring

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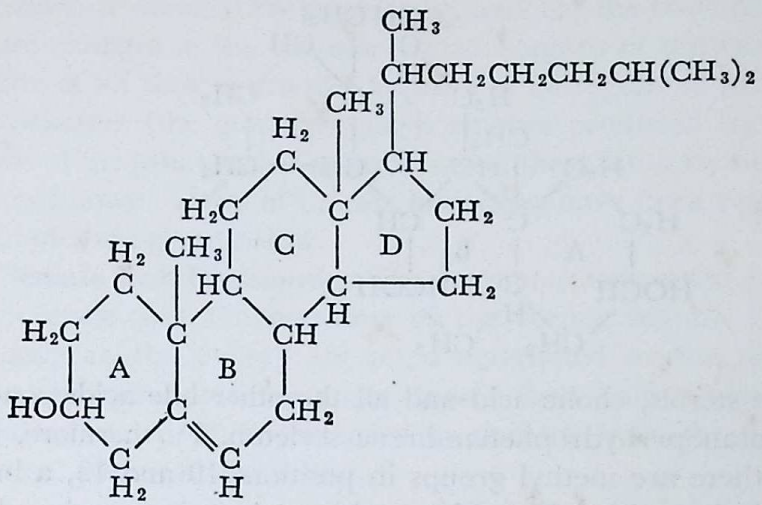
and a cylopentane ring fused together; an alternative name is therefore *cyclopentanoperhydrophenanthrene*.

Constitution of Cholesterol. The structural formula of cholesterol is:



Cholesterol

It will be noted that this formula contains the fused, hydrogenated phenanthrene-cyclopentane skeleton with methyl groups substituted at positions 10 and 13, a branched aliphatic chain at 17, an hydroxyl group at 3, and a double bond between atoms 5 and 6 in ring B. Almost all the sterols so far investigated differ from cholesterol only in regard to (1) the degree and position of the unsaturation (some are saturated); (2) the nature of the side chain on position 17; and (3) their stereochemical configuration. In regard to the latter point, an inspection of the formula will show that the same type of isomerism shown by the four isomeric decalols (p. 575) can occur in the sterols. Indeed, because of the number of rings, the possibilities are still greater. This fact, alone, makes an elucidation of the structure of these compounds a matter of great difficulty.

The Bile Acids. From the bile of various species of animals, a number of hydroxy acids have been isolated. They usually occur coupled to the amino acids, glycine, NH_2CH_2COOH, or **taurine,** $NH_2(CH_2)_2SO_3H$, through an amide linkage; thus, $RCONHCH_2$-CH_2SO_3H. The amide linkage is easily hydrolyzed and the unconjugated bile acids are obtained. Thus, **glycocholic acid** gives glycine (p. 354) and the bile acid, **cholic acid.** The latter, $C_{24}H_{40}O_5$ or $C_{23}H_{36}(OH)_3COOH$, occurs in large quantities in the bile of man

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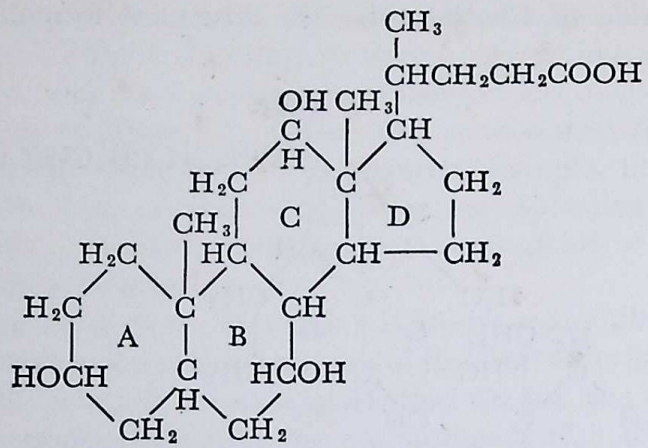
and a number of animals and is the commonest representative of this class. The structural formula for cholic acid is:



Like the sterols, cholic acid and all the other bile acids contain the cyclopentanoperhydrophenanthrene skeleton. Furthermore, like the sterols, there are methyl groups in positions 10 and 13, a branched side chain in position 17 (which in this case carries a carboxyl group) and position 3 carries an hydroxyl group. Unlike cholesterol, there is no unsaturation and there are two additional hydroxyl groups in positions 7 and 12, respectively.

SEX HORMONES AND VITAMIN D

The ductless glands of the animal body secrete internally substances known as *hormones*. These compounds are distributed by the blood or lymph to other portions of the body whose structure or function is thereby modified. The potency of these endocrine secretions (hormones) is remarkable, a very small portion of a milligram often being effective. Different glands produce different hormones with totally different physiological action. It is not surprising that among the hormones which have been isolated we find a variety of types of compounds.

One group of substances known as the *sex hormones* are closely related to cholesterol and the bile acids. Structurally, they may be considered as derived from cholesterol by oxidation. Indeed, it may be that cholesterol is the actual precursor of these hormones; but on this point we are still uncertain, and the way the animal body prepares these hormones is as yet unknown. The physiologist has recognized for years that the glands of the genital systems produce hormones. It is only recently, however, that by the combined labors of the

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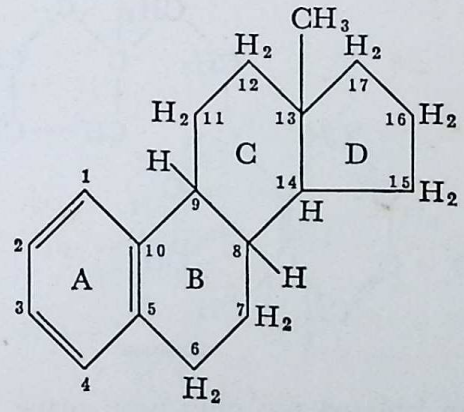
physiologist, biochemist, and organic chemist the sex hormones have been isolated and their structure determined. Three different types of sex hormones originate in the gonads (testes and ovaries). They are (1) the estrogenic hormones; (2) the hormone produced by the corpus luteum which is essential for pregnancy; and (3) the male hormones that cause changes in the accessory sexual organs of the male. The production of all these hormones appears to be regulated in turn by other substances (the gonadotropic hormones produced in the anterior lobe of the pituitary). The structure of these pituitary hormones is not now known. Those of the sex hormones have been established and examples are given below.

The Female Sex Hormones. The hormones concerned with the estrogenic cycle and the hormone of the corpus luteum (a small yellow body in the ovary) are often designated as the *female sex hormones*. The estrogenic hormones (more than half a dozen have been isolated) may all be regarded as derived from the following hypothetical parent hydrocarbon.



For example, one of the most potent of these hormones is **estriol,** which can be isolated from the urine of pregnant women. This substance is a trihydroxy derivative of the hydrocarbon shown above, the OH groups being at positions 3, 16, and 17. In a closely related ketone, **estrone,** which occurs along with estriol, there is a ketonic oxygen attached to carbon atom 17, and an hydroxyl at 3. (If the reader will write these formulas, it will become evident that on dehydration estriol should readily lose water between 16 and 17, yielding the enolic form of estrone. Actually, estrone is readily formed by dehydrating estriol.) Unlike the sterol and bile acid nucleus, that of the estrogenic hormones contains one aromatic ring. The hydroxyl group in position 3 is, therefore, phenolic (weakly acidic).

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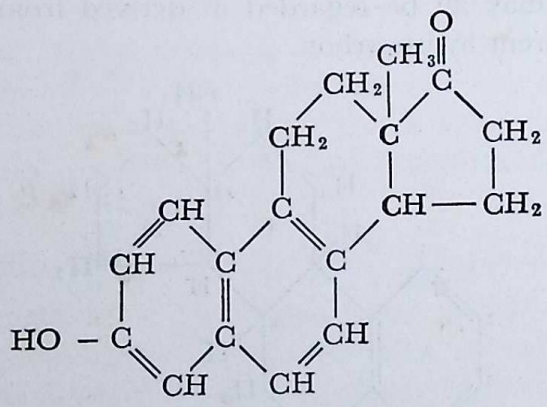
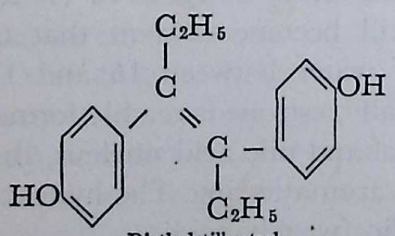
In printing structural formulas for the sex hormones, sterols, and related substances, various conventions are employed to save space. Instead of showing all the carbon and hydrogen atoms (as in the formulas on pp. 587 and 588), an outline formula may be printed and, as above, the hydrogen atoms shown *except in the aromatic rings*. This convention has been long employed with the terpenes. An alternative procedure is not to print any of the hydrogen atoms but show all the double bonds including those of the aromatic rings. The possibility of confusion between this convention and the one that employs an outline ring for an aromatic compound is evident. The reader of chemical literature must be on his guard, as three fused hexagons, for example, might signify either phenanthrene or perhydrophenanthrene!

A group of estrogenic hormones similar in structure to estrone has been isolated from mare's urine. One of these hormones, **equilenin,** has been synthesized. The hormone contains two asymmetric carbon atoms. The synthesis, of course, furnished only inactive material, but this material was resolved (p. 260) into the four active forms, one of which was identical with naturally occurring equilenin.

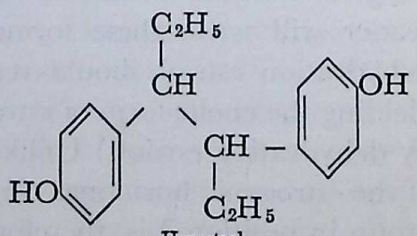


Equilenin

Estrone has been isolated not only from urine and placenta, but also from a variety of vegetable sources. It is interesting, in view of this lack of specificity of origin of estrone, that estrogenic activity is not specifically connected with the estrone type of structure. Thus the two synthetic compounds, **diethylstilbestrol** and **hexestrol,** only remotely related structurally to estrone, have estrogenic properties.



Diethylstilbestrol



Hexestrol

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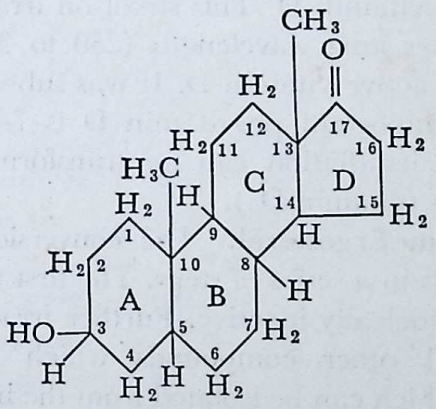
Progesterone, the hormone produced by the corpus luteum, is more closely related to cholesterol than the other female hormones. In this substance ring A is still alicyclic and the methyl group at position 10 intact. A ketonic oxygen is at position 3 and a double bond between 4 and 5; the other rings are saturated. At position 17 there is an acetyl group, CH_3CO-, representing a residuum of the side chain of cholesterol and the bile acids.

Male Sex Hormones. The two most important male hormones which can be isolated from urine and testicular extracts are **androsterone** and **testosterone.** Like progesterone, these compounds are more closely related to cholesterol than the female hormones. Androsterone contains the cholesterol structure with all four rings saturated, an hydroxyl group at 3 (secondary alcohol), and a ketonic oxygen at 17. In testosterone, a ketonic oxygen is at 3 and an hydroxyl (secondary alcohol) at 17 with a double linkage between atoms 4 and 5 in ring A. The male hormone structure seems to be much more specific than that of the estrogenic hormone.



Androsterone

Vitamins. Many careful experiments have shown that an animal may be fed on a diet which contains all the basal foods in a purified form, and yet the animal will fail to grow, become sick, and ultimately will die. This is true in spite of the fact that the components of the diet (purified proteins, fats, carbohydrates, mineral salts) are digested and metabolized by the animal. If now a few tenths of 1 per cent of certain materials are added to this diet, it becomes an entirely satisfactory ration and the animal survives. Such animal experiments form the basis of our knowledge of the accessory factors in the diet. These essentials have become known as the *vitamins*. By a process of repeated trial, it has been shown that there are a large number of

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vitamins which are necessary for a satisfactory diet; and by repeated feeding experiments, it has been possible to ascertain the concentration of these vitamins in certain foods. Several vitamins have been isolated and their structure has been determined. When a vitamin has been isolated its chemistry, as contrasted with its biochemistry, really begins. We have already had occasion to mention vitamin C (p. 292), vitamin K (p. 549), and vitamin A (p. 584).

Vitamin D. This vitamin is known as the antirachitic vitamin. Its absence in the diet interferes with the proper formation of bone tissue and continued vitamin D-free diet thus leads to rickets.

The first clue as to the nature of vitamin D was provided by the discovery that irradiation with ultraviolet light was beneficial to rickets. It was next found that the foodstuff might be irradiated instead of the patient. As soon as this fact was established, a chemical investigation of the foods was begun to discover what particular constituent was turned into vitamin D by the action of ultraviolet light. This substance proved to be **ergosterol** which can thus be considered as a provitamin D. This sterol on irradiation with ultraviolet light of rather long wavelength (250 to 300 mμ) was transformed into a very active vitamin D. It was subsequently discovered that a still more important provitamin D is 7-dehydrocholesterol. This substance on irradiation can be transformed into a slightly different vitamin D (vitamin D_3).

Vitamin D_2 from Ergosterol. The conversion of ergosterol to vitamin D_2 proceeds in a series of steps. The first two products which are formed are biologically inactive. Further irradiation of the vitamin produces still other compounds which are inactive. The active compound which can be isolated from the irradiated ergosterol under the most favorable circumstances is known as *vitamin D_2* or *calciferol*. It is isomeric with ergosterol but an investigation of the structure shows that ring B of the sterol system has been opened, the methyl group at position 10 being transformed into a methylene group ($=CH_2$). Ergosterol itself differs from cholesterol slightly in regard to the side chain and is more highly unsaturated. Rings A, C, and D are saturated but there is one double bond in the side chain and two in ring B. Ergosterol also contains one more carbon atom than cholesterol due to an additional methyl group in the side chain. Apparently the unsaturation of ring B is favorable to alteration by ultraviolet light. During irradiation the ring is opened.

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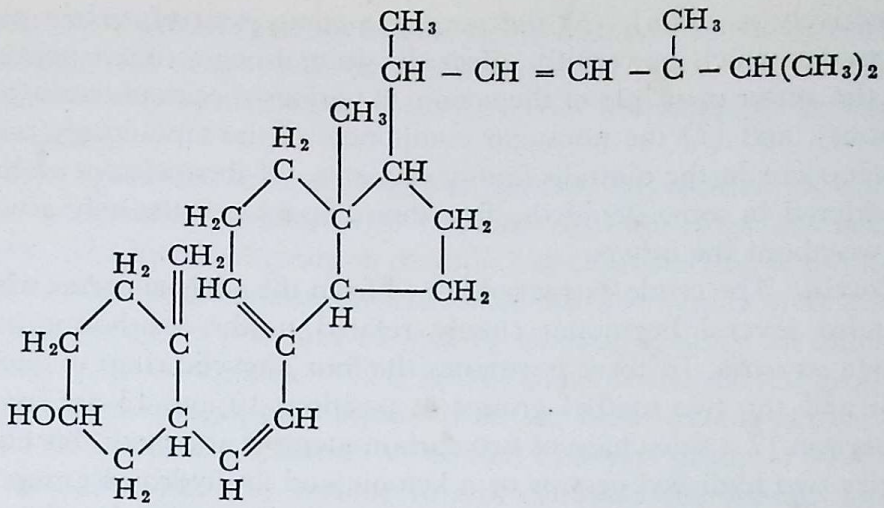

Calciferol
(vitamin D_3)

Vitamin D_3. It was at first thought that the vitamin D which occurs naturally in such materials as cod-liver oil was identical with the crystalline material obtained by irradiating ergosterol. This has turned out not to be so, however. The true vitamin in fish oils has been isolated and identified as being the compound prepared by irradiating a cholesterol transformation product called *7-dehydrocholesterol*. (*Dehydro* indicates less hydrogen.) 7-Dehydrocholesterol is, therefore, a provitamin D. 7-Dehydrocholesterol has a saturated side chain identical with that of cholesterol, saturated rings A, C, and D and, like almost all the sterols, a secondary alcohol group at position 3. There are two conjugated double bonds in 7-dehydrocholesterol just as there are in ergosterol and it is for that reason that it undergoes the same type of transformation with ultraviolet light. The vitamin D which is thus formed and which occurs in nature is called *vitamin D_3*. If one substitutes the saturated eight-carbon side chain of cholesterol for the unsaturated nine-carbon chain of vitamin D_2, the structural formula of vitamin D_3 results. (The name *vitamin D_1* was given to a substance which later proved to be a mixture; only two pure vitamin Ds are known, D_2 and D_3.)

OTHER COMPOUNDS OF BIOLOGICAL INTEREST CONTAINING THE CYCLOPENTENOPHENANTHRENE NUCLEUS

There are seven classes of compounds of interest to the biochemist which contain the carbon skeleton of cyclopentenophenanthrene. They are (1) the sterols, (2) the bile acids, (3) the sex hormones, (4) a group of hormones produced by the adrenal glands (known

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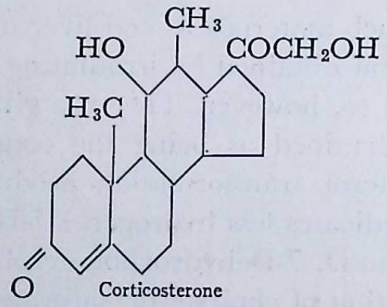
collectively as *cortin*), (5) the nonsugar component of certain plant glycosides which powerfully affect the animal heart (heart poisons), (6) the active principle of the venom of various species of toads (toad poisons), and (7) the nonsugar component of the saponin glycosides which occur in the digitalis family of plants. Of these classes we have considered in some detail the first three. Space permits only a word or two about the others.

Cortin. The crude extract obtained from the adrenal cortex which contains several hormones closely related to the sex hormones is known as *cortin*. In these hormones the four alicyclic rings of cholesterol and the two methyl groups at positions 10 and 13 are intact. At carbon 17 a side chain of two carbon atoms is attached; this chain carries two hydroxyl groups or a ketonic and an hydroxyl group. In addition there are two other oxygen atoms in the molecule.

The structure of **corticosterone** is shown below.



Corticosterone

These hormones are closely related to the sex hormones chemically and like them may be formed by the organism either by oxidation of a sterol or by some mechanism in the cell which builds a sterol-like molecule with a greater degree of oxidation and fewer carbon atoms than cholesterol.

Cardiac Aglucones. The plant heart poisons may be illustrated by considering the glycoside digitoxin obtained by extraction of the fresh leaves of members of the digitalis family (foxglove). The crystalline glycoside, **digitoxin,** $C_{41}H_{64}O_{13}$, on acid hydrolysis yields three molecules of the sugar, **digitoxose** (a modified aldohexose, $C_6H_{12}O_4$) and a nonsugar component **digitoxigenin,** $C_{23}H_{34}O_4$. The latter substance is known as a *genin* or *aglucone*. A dozen or so different aglucones have been obtained by the hydrolysis of a variety of physiologically active glycosides. In the plant tissues even more complicated glycosides occur for it has been shown that digitoxin itself is the product of a hydrolytic reaction which occurs during isolation, a

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molecule of glucose and acetic acid being split off. The aglucones are less powerful drugs than the glycosides and much less soluble in water. The preparations used in medicine are mixtures of various glycosides.

The aglucones derived from the **cardiac glycosides** all contain the cyclopentenophenanthrene nucleus. All four rings are nonaromatic. The hydroxyl group in position 3 so characteristic of the sterols and sex hormones is also present in all but one instance, as are the methyl groups in positions 13 and 10 (in one instance an aldehydo group $-CHO$ replaces $-CH_3$ at 10). The characteristic grouping of the cardiac aglucones seems to be an unsaturated lactone ring (p. 610) attached to position 17 and an hydroxyl group at 14.

Toad Poisons. In various species of toads the glands located behind the eyes secrete a poisonous material. This has long been known and the crude dried preparation has been used as a drug in China for centuries. The physiologically active compound occurs combined with an amino acid (Chap. 19). On hydrolysis, the nonnitrogenous compound is liberated. As in the cardiac glycosides, the substance produced by hydrolysis is called a *genin*. Several such genins have been prepared in a pure state and their structure wholly or in part determined. The cyclopentenophenanthrene skeleton has been shown to be present, all four rings being nonaromatic. Like the heart poisons, an unsaturated lactone is attached to carbon atom 17 and one or more hydroxyl groups are present at different points in the molecule; positions 10 and 13 each carry methyl groups. In short, except for the side chain, the characteristic features of the sterol molecule are repeated.

Saponins. Certain substances which occur fairly widely distributed in plants have the property of forming a type of colloidal solution in water which foams on shaking like a soap solution. These materials are known as *saponins*. A few of them find limited uses in medicine and industry as foam producers. They are not a closely related group of compounds either biologically or chemically but the striking characteristic of their aqueous solutions has resulted in a diversity of compounds being classed together. They are all glycosides and on hydrolysis the nonsugar component (called a *sapogenin*) may be isolated.

Three sapogenins which may be prepared from the saponins extracted from the plants of the digitalis family are of special interest as they have been found to be related to the sterols. Their structures contain the usual cholesterol skeleton (including the two methyl groups at positions 10 and 13 and an hydroxyl group at 3). The side chain contains seven carbon atoms with cyclic ether linkages involving two oxygen atoms. All rings are completely saturated. Since saponins from at least two other families of plants besides the digitalis have yielded the same or similar genins,

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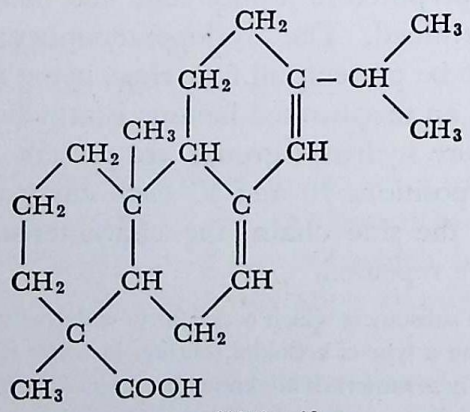
this type of structure is apparently not confined to one genus. The saponin (i.e., glycoside) **digitonin** (from digitalis) has the rather remarkable ability to form a sparingly soluble molecular compound with cholesterol. A number of other sterols having in position 3 a free hydroxyl group with the same stereochemical configuration as cholesterol are also precipitated as stable molecular compounds with digitonin. This reaction has been very useful in isolating and characterizing sterols. Probably closely related to this affinity for cholesterol is the fact that digitonin and related saponins have a powerful hemolytic action, that is, they break the membrane of the red blood cells, perhaps by combining with cholesterol or similar substances in the membrane.

Another group of sapogenins are more closely related to the sesquiterpenes (p. 584). On selenium dehydrogenation they yield 1,2,5-trimethylnaphthalene. They contain thirty carbon atoms, thrice the number present in the terpenes and hence are designated as *triterpenes*. Certain acids of plant origin appear to belong to this same class of substances.

Rosin. The residue left behind in the manufacture of turpentine by distillation (p. 581) is a solid known as *rosin* or *colophony*. It is a mixture of **abietic acid,** $C_{19}H_{29}COOH$, and its anhydride. Abietic acid contains a partially hydrogenated phenanthrene nucleus. It is thus related to the sterols and, because the molecule can be divided up into four isoprene residues (p. 584), to the terpenes. Since abietic acid has a high molecular weight, its sodium and potassium salts have soaplike properties, and it is frequently used in connection with the manufacture of soap. It is also used in the manufacture of varnishes and, with alum, it is employed as sizing for paper.



Abietic acid

QUESTIONS AND PROBLEMS

1. Write structural formulas for isoprene, dipentene, cholesterol, phytol, Vitamin D_3, and abietic acid.

2. What structural features of abietic acid are consistent with the fact that its alkali salts are detergents? Compare abietic acid with some detergents encountered earlier in this book.

3. State the isoprene rule and give illustrations of its usefulness.

4. Define and illustrate the following terms: *sterols*, *terpenes*, *hormones*, *sesquiterpene*, *vitamins*, *saponins*, *aglucones*, *sapogenins*, *bile acids*.

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5. What reactions (if any) would you expect when the following substances are treated with (*a*) a dilute carbon tetrachloride solution of bromine, (*b*) methylmagnesium iodide in ether solution, (*c*) maleic anhydride and heat: vitamin D_3, dipentene, menthol, cholesterol, the ester of cholic acid.

6. A number of the terpenes containing fifteen carbon atoms can be converted to a dimethyl-isopropyl-naphthalene known as *cadalene*. On the basis of the isoprene rule can you show that 1,6-dimethyl-4-isopropylnaphthalene is a more likely structure for cadalene than is 1,8-dimethyl-4-isopropylnaphthalene?

7. Lithocholic acid, $C_{24}H_{40}O_3$, is a bile acid which differs from cholic acid in that it contains one hydroxyl group instead of three. The hydroxyl group is in position three. Write the structural formula. On dehydration and catalytic hydrogenation what product or products would you expect to obtain? On dehydrogenation of the secondary alcohol group and hydrogenation to regenerate this group how many isomers would you expect to obtain?

8. Devise a method for: (*a*) replacing the hydroxyl group of a sterol by hydrogen, (*b*) protecting the hydroxyl group during oxidation of the molecule at another point, (*c*) proving the hydroxyl group was that of a secondary alcohol.

9. Name and write structural formulas for two synthetic substances which have marked estrogenic activity. Compare their structures with that of estrone.

10. Cholic acid when heated in a vacuum loses three molecules of water. The resulting unsaturated acid when hydrogenated furnishes cholanic acid, $C_{23}H_{39}COOH$, which contains four completely saturated rings. Write the structural formula for cholanic acid and show all the steps in the degradation of the side chain by the method which employs phenylmagnesium bromide.

11. Outline the steps in the synthesis of *p*-cymene from benzene.

12. What reactions would you use to prove (*a*) that cholesterol contains a secondary hydroxyl group, (*b*) that it contains a double bond, and (*c*) that the double bond is in the following position in relation to the hydroxyl group: $HOCH - CH_2 - C = C$?

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Chapter 31

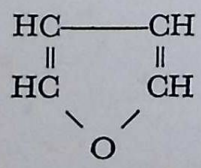
HETEROCYCLIC COMPOUNDS

Cyclic compounds which contain two or more different elements in the ring are known as *heterocyclic compounds*. The elements which are commonly found together with carbon in ring systems are oxygen, sulfur, and nitrogen. We have already encountered a number of heterocyclic compounds in connection with our study of aliphatic chemistry. For example, lactones, cyclic anhydrides, cyclic imides, and the cyclic forms of the sugars are all heterocyclic compounds. Such substances, which are closely related to the aliphatic compounds, are usually considered in connection with aliphatic chemistry and require no separate treatment. There are other heterocyclic compounds, however, which resemble the aromatic hydrocarbons in their unsaturation and in their properties. The first part of this chapter is devoted to an elementary survey of the more important representatives of these aromatic heterocyclic compounds. This is followed by a brief survey of a few of the more complex condensed heterocyclic systems. And both in this chapter and the one to follow, references are made to a number of important naturally occurring substances which contain heterocyclic rings.

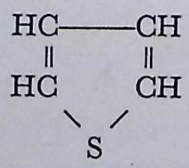
AROMATIC HETEROCYCLIC COMPOUNDS

The commoner heterocyclic compounds are derivatives of the following substances, each of which is to be regarded as the simplest representative of a large class.

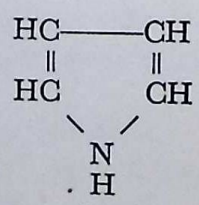
1. Five-membered rings.



Furan
bp 32°



Thiophene
bp 84°



Pyrrole
bp 130°

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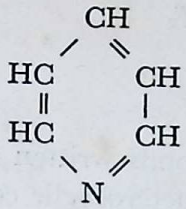
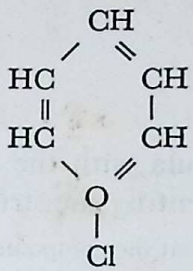
2. Six-membered rings.

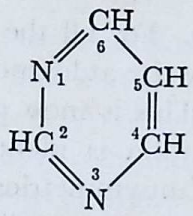


Pyridine
bp 115.5°

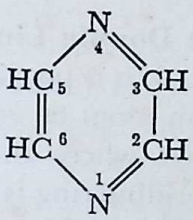


Pyrylium chloride
(a salt)

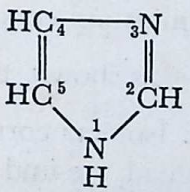
3. Five- and six-membered rings with more than one atom other than carbon.



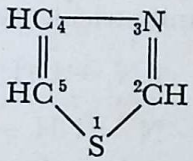
Pyrimidine
bp 124°



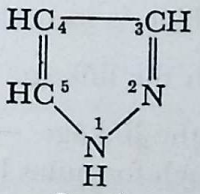
Pyrazine
bp 115°



Imidazole
bp 255°



Thiazole
bp 117°



Pyrazole
by 187°

The position of substituents is indicated in the systems of classes 1 and 2 by numbering the ring starting with the nitrogen, oxygen, or sulfur atom and proceeding counterclockwise (as the formulas are usually written). Another method is to designate the atoms on both sides of the ring immediately adjacent to the "hetero-atom" as α, the next β, and in the six-membered ring, the atom at the opposite end as γ. The numbering of the rings in the system of class 3 is shown in the formulas themselves. Substituents on nitrogen are usually designated by the letter N before the substituent. Thus N-methyl-2,3-dimethyl-4-ethyl pyrrole or N-methyl-α,β-dimethyl-β'-ethyl pyrrole has the formula:

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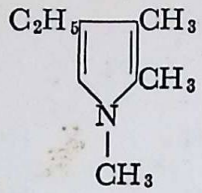
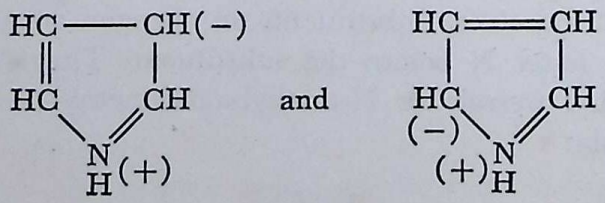


An outline formula with the double bonds written in, is often employed in representing the structure of heterocyclic compounds.

It will be noted that the compounds in group 3 may be regarded as derived from those in groups 1 and 2 by substitution of $-N=$ for a CH group. All the possibilities are clearly not exhausted by the above list and other types of aromatic heterocyclic compounds containing oxygen, sulfur, and nitrogen are known. The five-membered rings containing two nitrogen atoms are known as the *azoles*, the six-membered rings as the *azines*. Instead of the trivial names listed above the structure may be indicated by numbers thus: pyrimidine is 1,3-diazine, pyrazine is 1,4-diazine.

Position of the Double Linkages. For all the compounds listed in groups 1, 2, and 3, it is possible to write at least one other structure without shifting an atom or group. This is most clearly seen in the six-membered rings where the situation is identical with that in benzene. If the pyridine ring is made unsymmetrical, for example, by the introduction of a substituent on the atom adjacent to nitrogen, two isomeric arrangements of the linkages may be written. In pyrimidine, which is in itself unsymmetrical, two formulas are conceivable, one with the linkage $-\overset{6}{CH}=\overset{1}{N}-\overset{2}{CH}=\overset{3}{N}-$ as shown, the other having the linkage $-\overset{6}{CH}-\overset{1}{N}=\overset{2}{CH}-\overset{3}{N}=$. Isomers corresponding to such formulas have never been found. Instead, we find that the substance has a pronounced stability compared to open-chain compounds or ring systems where such possibility of shifting bonds does not occur. This is due to *resonance* already discussed in connection with guanidinium salts (p. 338) and benzene (p. 405).

With the five-membered rings the alternative structures involve the assumption that a negative charge may be localized on a carbon atom while the oxygen, nitrogen, or sulfur is positive. Compare the structure of the amine oxides (p. 194) and isonitriles (p. 195). For example, pyrrole could have the following structures.



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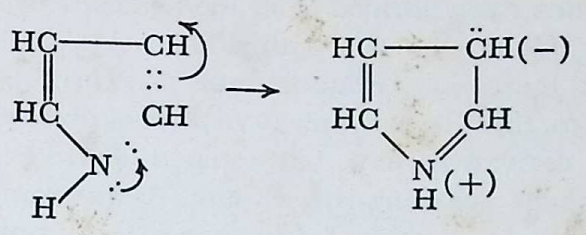
The following electronic shift occurs in the change from the structure shown in the usual formula to that shown in the formula to the left above (only the electrons involved are shown).



This should be compared with the shift involved in the resonance of guanidine (the free base) and of the undissociated carboxyl group, and the full electronic formulation given on page 81 should be consulted.

The increased stability due to resonance of such five-membered heterocyclic compounds as furan, thiophene, and pyrrole is considerable, but is less than that of the six-membered rings. The resonance energy of these three five-membered heterocyclic systems is about 24 to 29 kg-cal, that of pyridine about 43 kg-cal. As a consequence the energy relation between furan and dihydrofuran is in between that of an unsaturated open-chain compound and benzene. Thus the reaction, furan + $H_2 \longrightarrow$ dihydrofuran, is exothermic by 11 kg-cal. (Compare benzene, where the corresponding reaction is endothermic by 6 kg-cal.) Because the reaction is of the type $A + B \longrightarrow AB$, the equilibrium constant for the first step in the hydrogenation of furan is about unity.

Reduced Heterocyclic Compounds. A great variety of heterocyclic compounds are known which may be regarded as partial or complete hydrogenation products of the substances just considered. They correspond to the alicyclic compounds. It will be evident that the addition of two or more hydrogen atoms to any of the systems we have so far considered will yield a substance with one or more CH_2 groups. A great variety of such compounds and their derivatives are known. Since many of them (e.g., lactones, cyclic ethers, and anhydrides) are derived from open-chain compounds, they are usually considered in connection with aliphatic chemistry. When such substances differ from the heterocyclic aromatic compounds by only one pair of hydrogen atoms, they are often easily dehydrogenated as are the corresponding alicyclic compounds.

Methods of Preparation. Heterocyclic compounds are prepared either by condensation reactions which lead to ring formation or by

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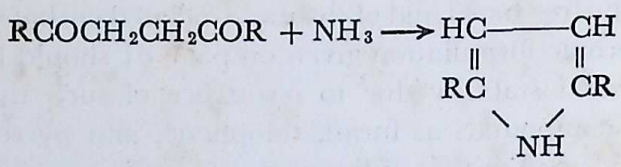
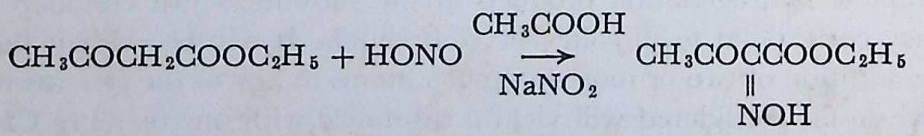
transformations of readily accessible substances which contain the heterocyclic ring in question. Thus a number of simple furan derivatives may be prepared from the furan aldehyde, **furfural** (p. 285), which is in turn easily formed from the pentoses. By distilling bran, corncobs, or similar material with dilute acids, furfural is formed. It is prepared industrially from oat hulls and corncobs.

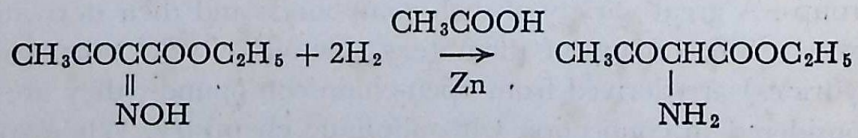
Unlike furan, there is no simple derivative of pyrrole available from which other derivatives may be prepared. Pyrroles are, therefore, made by methods involving ring closure. As an example, the formation of pyrroles by heating 1,4-diketones with ammonia may be mentioned.

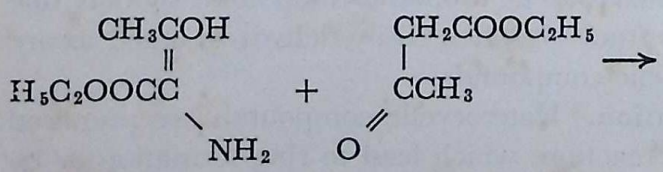


Substituted furans may also be made from 1,4-diketones by heating with dehydrating agents. It is believed that this reaction proceeds by the elimination of water from the dienol of the diketone.

A much more important ring-closure reaction for pyrroles is the series of reactions known as *Knorr's pyrrole synthesis*. Acetoacetic ester, or a related compound containing a reactive methylene group, is treated with acetic acid and sodium nitrite to convert the CH_2 to $C = NOH$. The resulting oximino compound is reduced with zinc and acetic acid to the corresponding amine. The reduction is run in the presence of excess acetoacetic ester so the amine condenses to form the pyrrole as fast as it is formed.







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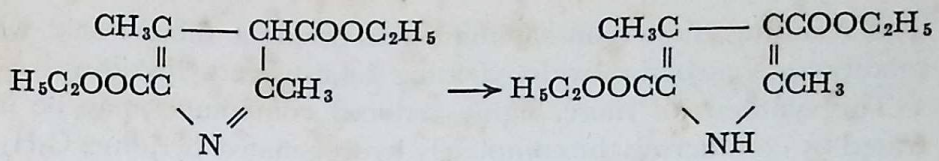
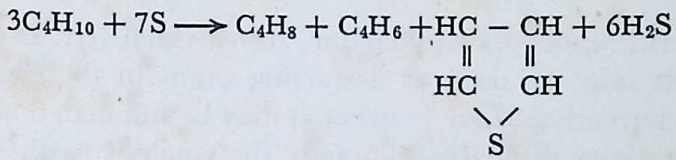


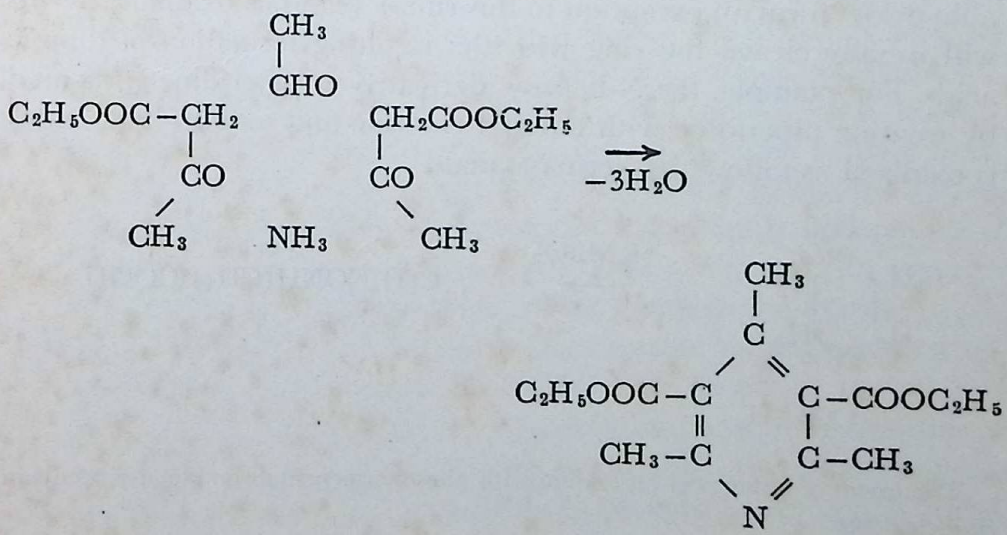
In spite of the apparent complexity of the process, it works very well. It is not necessary to isolate the intermediate products. This method was used to synthesize the pyrroles obtained by the degradation of chlorophyll and hemoglobin (p. 624).

Thiophene is prepared by the reaction between butane (from the C_4 cut from petroleum cracking, p. 119) and sulfur. These two reactants on short contact at about 600° yield butene, butadiene, thiophene, and hydrogen sulfide.



Derivatives of thiophene can be prepared from the parent substance by reactions similar to those employed with benzene—halogenation, nitration, sulfonation, and the Friedel-Crafts reaction.

Substituted pyridines are formed when beta ketonic esters, an aldehyde, and ammonia are allowed to interact. This reaction may be illustrated with acetaldehyde and acetoacetic ester. It shows how several molecules may interact in what appears to be an extremely improbable manner in order to produce a relatively stable, heterocyclic, aromatic compound.



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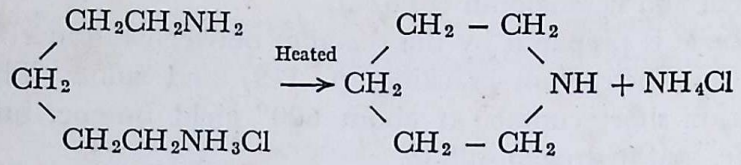
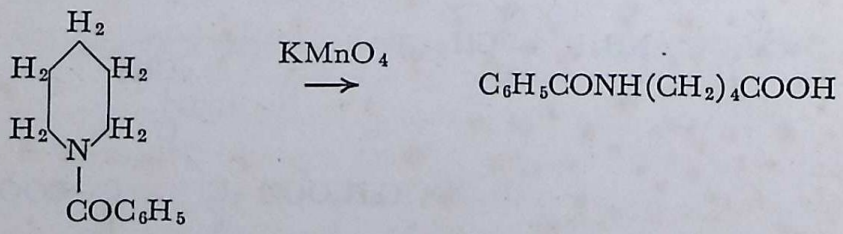
The resulting diester on saponification yields a dibasic acid which readily loses carbon dioxide, yielding 2,4,6-trimethylpyridine.

The synthesis of more highly reduced compounds may be illustrated by considering the completely hydrogenated pyridine, $C_5H_{11}N$, **piperidine.** This compound may be synthesized either by reducing pyridine with sodium and ethyl alcohol or by heating an open-chain diamine.



Since pyridine occurs in coal tar, from which it is isolated commercially, it may be used as a starting point in the synthesis of a number of derivatives. Like benzene it may be sulfonated and nitrated but with greater difficulty. Though the analogy with benzene is striking, it cannot be pressed too far, particularly with such five-membered rings as pyrrole. Indeed, as far as specific reactions are concerned each one of the ring systems listed on pp. 598-599 has a chemistry of its own just as does benzene, naphthalene, and anthracene.

Opening Heterocyclic Rings. For the purpose of determining structure, it is important to be able to transform cyclic compounds into open-chain derivatives. In general, the aromatic heterocyclic compounds and their reduction products contain rings which are opened with difficulty. (The lactones and cyclic imides, amides, and anhydrides form an exception to this rule.) Vigorous oxidizing agents will usually cleave the ring with the resulting formation of dibasic acids. For example, the N-benzoyl derivative of piperidine (prepared by treating piperidine with benzoyl chloride and sodium hydroxide) is oxidized as follows by permanganate.



Treatment of N-benzoyl piperidine with phosphorus pentabromide also results in ring cleavage.

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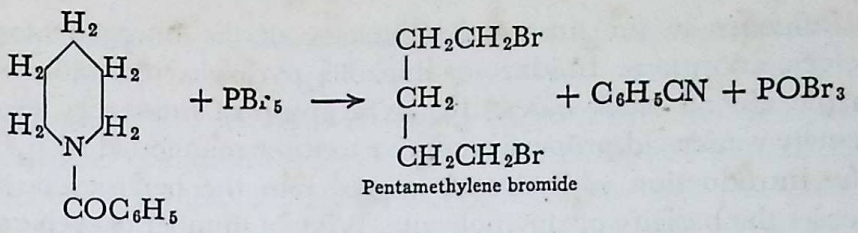
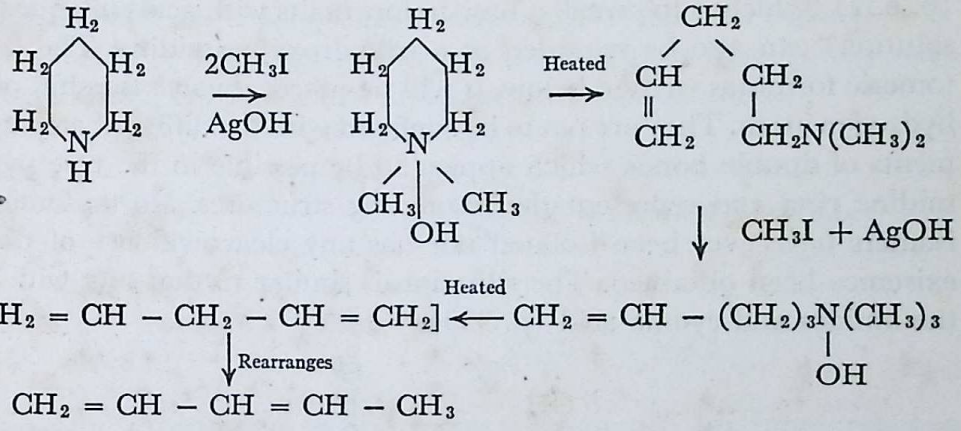


Exhaustive Methylation. A very important method of opening nitrogen-containing rings which has been much employed in determining the structure of alkaloids (p. 628) depends on the thermal decomposition of quaternary ammonium bases (p. 193). An application of this reaction to piperidine is as follows:



Basic and Acid Properties. Pyrrole and its derivatives are both extremely weak acids and extremely weak bases. In aqueous solution neither property is evident, as the salts are completely hydrolyzed. Only in nonaqueous solvents may the hydrogen of the NH group be replaced by such a metal as potassium. When pyrrole and potassium hydroxide are heated in the absence of water, for example, the potassium derivative is formed. Like the amides, and unlike the amines, the tendency for the nitrogen of pyrrole to pass into the ammonium form is very slight. On the other hand, the reduction product of pyrrole, **pyrrolidine** C_4H_9N, has the basic strength of an ordinary secondary amine and has none of the acidic properties of pyrrole. It is clear that the two double bonds in the pyrrole ring have much the same effect on the nitrogen atom as the presence of the carbonyl group in amides (see phthalimide, p. 509).

Pyridine is a weak base with a dissociation constant of the same order of magnitude as aniline (see diagram, p. 188). Its reduction product, piperidine, however, is comparable in strength to the aliphatic amines.

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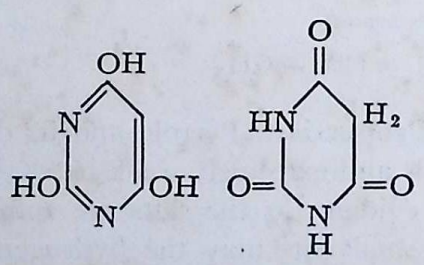
The influence of the unsaturated linkage of the nitrogen atom is, therefore, enormous. Imidazole, thiazole, pyrazole, pyrimidine, and pyrazine are all weak bases. The NH group of imidazole also has extremely weak acid properties similar to those manifested by pyrrole.

The introduction of hydroxyl groups into the heterocyclic rings decreases the basicity of the molecule. When a number of such groups are present the compound is usually too weak a base to form salts which are stable in aqueous solution. This may be interpreted as an effect of the hydroxyl group on the heterocyclic aromatic ring or by supposing that the compounds exist largely (or entirely) in the tautomeric form. For example, it will be noted that barbituric acid (p. 331) (which is too weak a base to form salts with acids in aqueous solution) can also be regarded as a trihydroxypyrimidine. The tautomeric formulas written below, it will be noted, involve the shift of a hydrogen atom. They are not to be confused with the different arrangements of double bonds which appear to be possible in the true pyrimidine ring and represent the resonating structures. No tautomeric isomers have ever been isolated nor has any clear evidence of their existence been obtained. The situation is similar to that met with in the amides and cyanic acid (p. 333).



Tautomeric forms of trihydroxypyrimidine (malonyl urea or barbituric acid)

The acid properties of the hydroxyl derivatives of heterocyclic compounds increase, as a rule, with the number of hydroxyl groups. If the formula with hydroxyl groups is correct, these compounds are analogous to phenols. They are stronger acids than simple phenols, however. Barbituric acid, for example, is comparable in strength to acetic acid.

Both tautomeric formulas of such compounds as barbituric acid correspond to systems with considerable resonance energy. The trihydroxy form contains a pyrimidine ring which can resonate as does the ring in benzene. The malonyl urea form would manifest the same type of resonance as urea (p. 328). It is impossible at present to conclude with assurance which of the two forms should be more stable in aqueous

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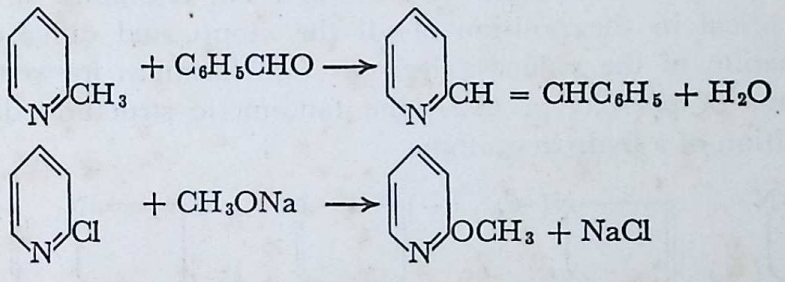
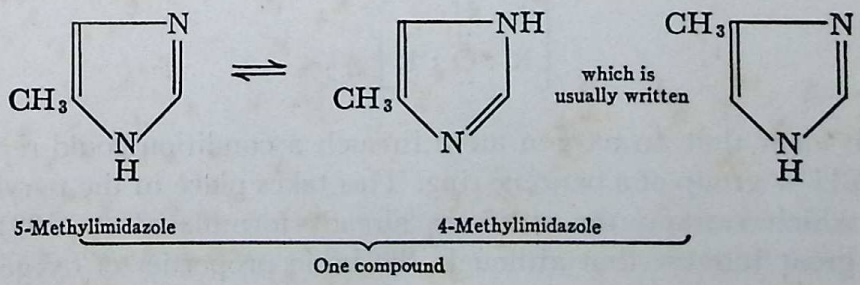
solution. Perhaps a very mobile equilibrium is present between the two tautomeric resonating systems.

Behavior of Substituents in the 2 and 4 Positions in Pyridine and Similar Compounds. A very useful empirical generalization enables us to correlate a great deal of information about the chemical behavior of those heterocyclic compounds which, like pyridine, contain a C = N linkage in the ring. The C = N linkage resembles the C = O linkage more than the C = C linkage. Atoms or groups in the alpha or gamma positions of a heterocyclic system containing a C = N linkage behave qualitatively as if they were attached to a C = O group. Another way of stating the same generalization is that *substituents in the ortho or para position in heterocyclic rings containing a* C = N *linkage behave as if they were ortho or para to a nitro group in the benzene ring.* The following equations will illustrate the generalization.



The same substituents in the meta position are no more reactive than they would be in benzene.

Tautomerism of Imidazole and Pyrazole. Imidazole and pyrazole contain both an >NH and a = N − linkage. The interchange of hydrogen between the two nitrogen atoms in both types of rings is very rapid. If the ring in imidazole, for example, is made unsymmetrical by the introduction of a methyl group, two isomers might be expected according to whether the group is adjacent to the >NH or = N − . Such isomers have never been isolated. We are dealing here as in cyanic acid with two tautomeric forms.



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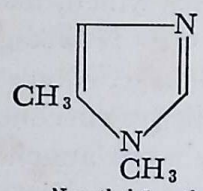
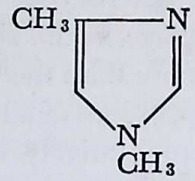
For this reason the 4 and 5 positions are identical in the imidazole ring. Similarly the 3 and 5 positions are identical in pyrazole. If, however, the hydrogen atom on nitrogen is replaced by a methyl group, a tautomeric shift is no longer possible and the following isomers, for example, can be readily obtained.

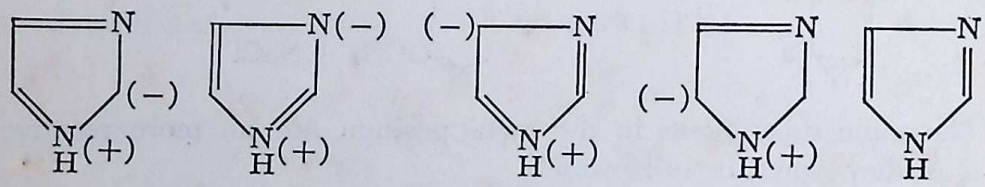


N-methyl-5-methyl-imidazole



N-methyl-4-methyl imidazole

It is important to distinguish the tautomeric shift in the imidazole and pyrazole rings from the resonance of these rings. The resonating structures are identical in the position of all the atoms, and differ only in the location of the valency electrons (see formulas for resonating structures of pyrrole, p. 600); the tautomeric structures differ in the position of a hydrogen atom.



Resonating structures of imidazole

Pyrones and Pyrylium Salts. The six-membered ring containing one oxygen atom requires a few words of special mention. Since oxygen normally has a valence of 2, unlike nitrogen it can not replace a $-CH=$ group in an aromatic six-membered ring. In nonaqueous solution, ethers (ROR) can form salts with acids, oxygen becoming formally quadrivalent but actually having only three atoms or groups attached by covalent bonds (p. 195).

$$\left[R : \overset{H}{\underset{..}{\overset{..}{O}}} : R \right]^{+} Cl^{-}$$

It is clear that an oxygen atom in such a condition could replace a $-CH=$ group of a benzene ring. This takes place in the pyrylium salts which contain the structure already formulated (p. 599). It is of great interest that although the basic properties of oxygen in

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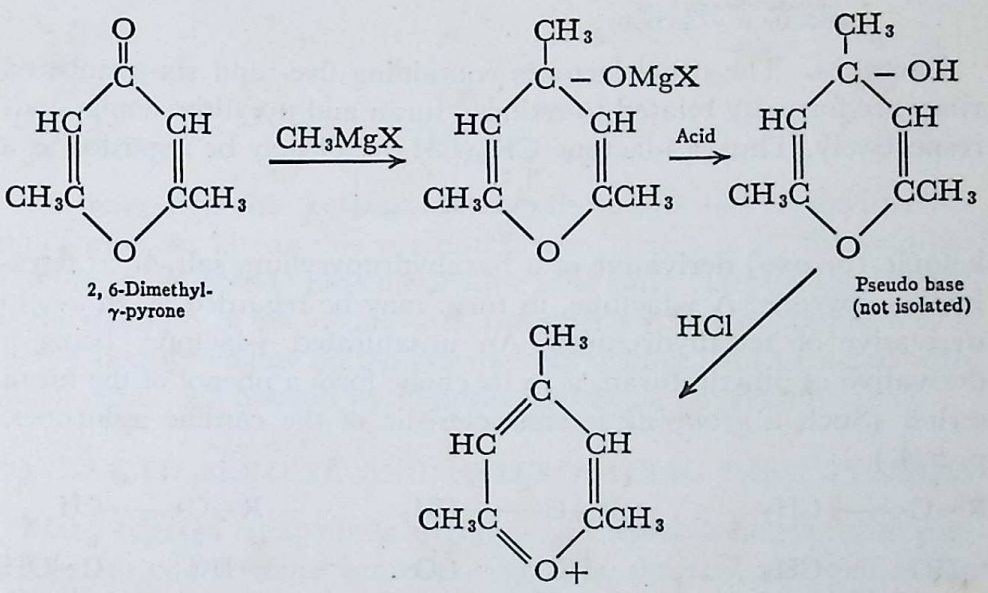
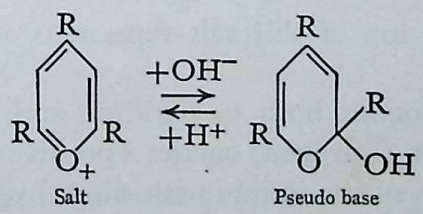
the usual types of compounds (i.e., ethers, ketones, etc.) are so weak that they are not manifested in dilute aqueous solution, the pyrylium salts are stable in water. This is a striking illustration of the relative stability of an aromatic ring and may be explained nicely in terms of resonance.

Pyrylium salts without substituent groups are unknown. Trimethylpyrylium chloride may be prepared from 2,6-dimethyl-γ-pyrone by the following reactions.



When treated with alkali, pyrylium salts are converted into compounds with an hydroxyl group in the α or γ position known as *pseudo bases*. On treatment with acid, the pseudo bases form pyrylium salts. The reaction has been studied most extensively with the triaryl pyrylium salts, for example, triphenylpyrylium chloride. A pseudo base is an intermediate in the synthesis of trimethylpyrylium chloride given above.



The pyrones in which the ketonic group and oxygen bridge are opposite are known as *γ-pyrones;* those in which the CO group is adjacent to the oxygen are called *α-py-*

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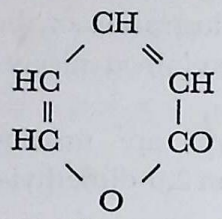
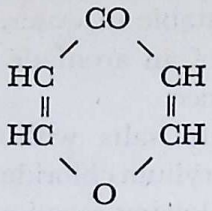
rones. An inspection of the formula of α-pyrone (below) shows that it is the δ-lactone of an unsaturated acid.

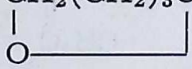


α-Pyrone
(δ-lactone of enolic form of $CHOCH_2CH = CHCOOH$)

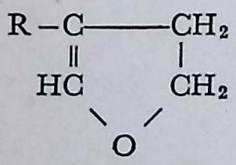


γ-Pyrone

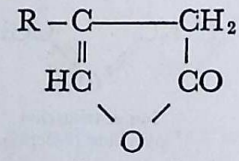
Lactones. The usual lactones containing five- and six-membered rings are formally related to reduced furan and pyrylium compounds respectively. Thus, a δ-lactone $CH_2(CH_2)_3CO$ may be regarded as a



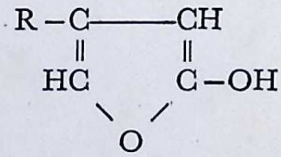
ketonic (or oxo) derivative of a hexahydropyrylium salt, or as tetrahydro-α-pyrone. A γ-lactone, in turn, may be regarded as an α-keto derivative of tetrahydrofuran. An unsaturated γ-lactone, being a derivative of dihydrofuran, is in its enolic form a phenol of the furan series. (Such a grouping is characteristic of the cardiac aglucones, p. 594.)



Dihydrofuran



Unsaturated γ-lactone



Enolic form of unsaturated γ-lactone

It should be carefully noted that the lactone ring (saturated or unsaturated), unlike almost all other heterocyclic rings, is easily opened by hydrolytic agents.

Pyridinium Compounds. Pyridine, being a tertiary amine, can add 1 mole of an alkyl halide forming a quaternary ammonium salt, $C_5H_5N\begin{matrix}CH_3\\ \\ I\end{matrix}$. The ion of this salt represents still another type of aromatic ring, analogous both to pyridine and the pyrylium salts; the heterocyclic atom (nitrogen) carries a positive charge. On treating the aqueous solution of the iodide with silver hydroxide, the quaternary base is formed. This is a strong base (compare tetramethyl

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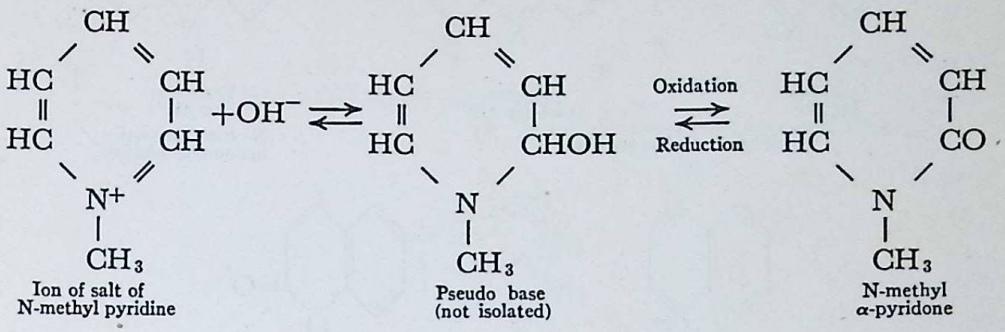
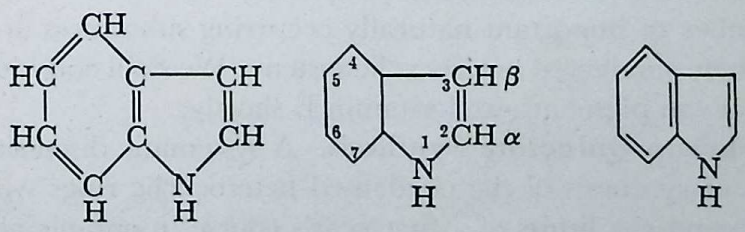
ammonium hydroxide). Since the compound is easily oxidized by potassium ferricyanide to N-methyl-α-pyridone, it is probable that some pseudo base is in equilibrium with the free base.



The only difference between the pyrylium salts and N-alkyl pyridinium salts, so far as this reaction is concerned, is in the relative stability of the pseudo base in alkaline solutions. Depending largely on the solubility of the pseudo base, the heterocyclic compounds which carry a positive charge on the hetero atom behave, when treated with alkali, either like N-alkyl pyridinium salts or like pyrylium salts.

CONDENSED BENZENE AND HETEROCYCLIC RING SYSTEMS

Many types of compounds are known in which a heterocyclic ring is fused to one or more benzene rings. The simplest and one of the most important representatives of this large class of substances is **indole,** a product of decomposition of certain proteins. To illustrate the conventions employed in writing the structural formulas of this substance, three methods of writing the formula of indole are given below.



Indole
solid, mp 52°

The nomenclature of substituents is indicated by the numbering of the central formula.

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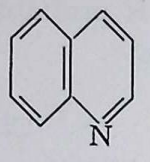
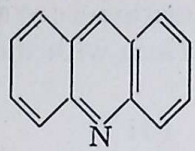
Some Representative Condensed Heterocyclic Compounds

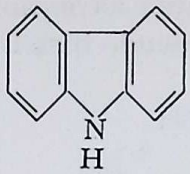


Quinoline
bp 239°



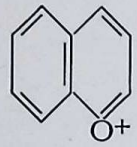
Acridine
solid, mp 110°

Weak bases like pyridine

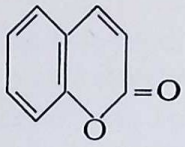


Carbazole
mp 238°

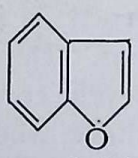
No basic properties in aqueous solution



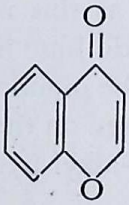
Ion of benzopyrylium salts



Coumarin (a lactone)
(See p. 489)



Coumarone (benzofuran)
bp 170°



Chromone

In their chemical reactions these condensed systems for the most part show the characteristic reactions of both the benzene and the heterocyclic ring. Except for the lactone, coumarin, the heterocyclic ring is remarkably stable. In quinoline and acridine the properties of the six-membered rings are modified by the pyridine nucleus to which they are fused. Thus, like naphthalene and anthracene, these substances deviate to some extent in their behavior from the reactions characteristic of the monocyclic compounds.

A number of important naturally occurring substances are derivatives of these condensed heterocyclic systems. We shall consider indigo, the anthocyan pigments, and vitamin E shortly.

The Skraup Quinoline Synthesis. A systematic discussion of the methods of synthesis of the condensed heterocyclic rings would take us far beyond the limits of a first year's course in organic chemistry. We shall, therefore, merely give by way of illustration one method of synthesizing quinoline derivatives, the Skraup synthesis. This consists in heating a mixture of aniline and glycerol with strong sulfuric acid and an oxidizing agent such as arsenic acid. Acrolein (p. 317) is

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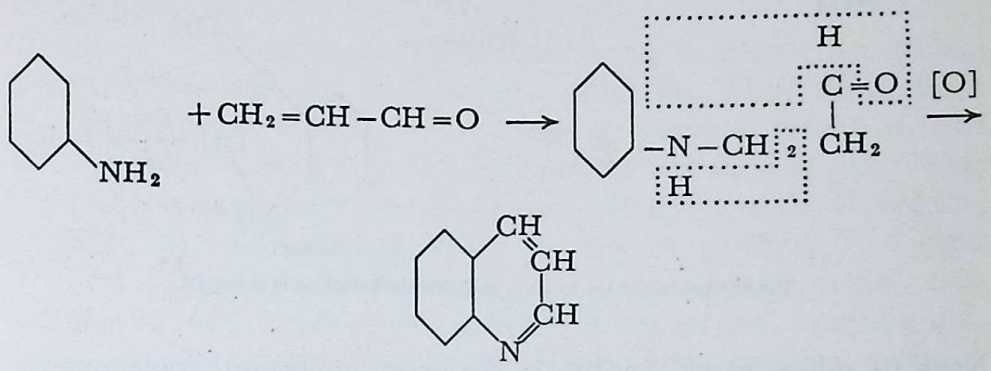
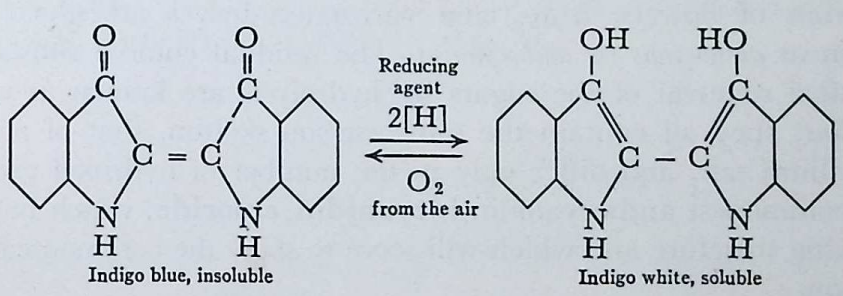
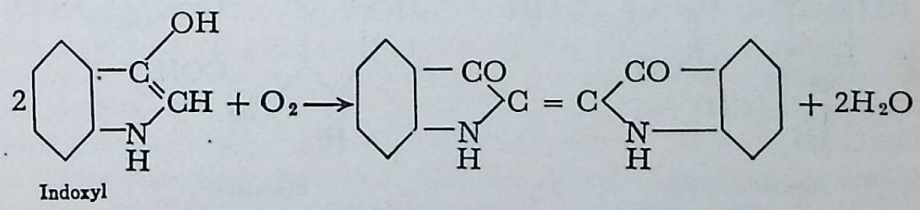
probably formed as the first product, which then condenses with aniline (1,4 addition) and under the influence of the oxidizing agent closes the heterocyclic ring.



Indigo. Indigo, the oldest known vat dye, is a derivative of indole. Vat dyeing with indigo may be represented by the following equation. The similarity to the anthraquinone vat dyes (p. 555) in chemistry and method of application should be obvious.



A number of semitropical plants contain the glucoside **indican**. On hydrolysis, indican furnishes glucose and indoxyl. This latter substance is oxidized to indigo by exposure to atmospheric oxygen.



Indigo was obtained from plants for hundreds of years. In 1882, however, Baeyer established the structure of indigo, and methods of synthesis were soon developed. At present the phenylglycine synthesis is used.

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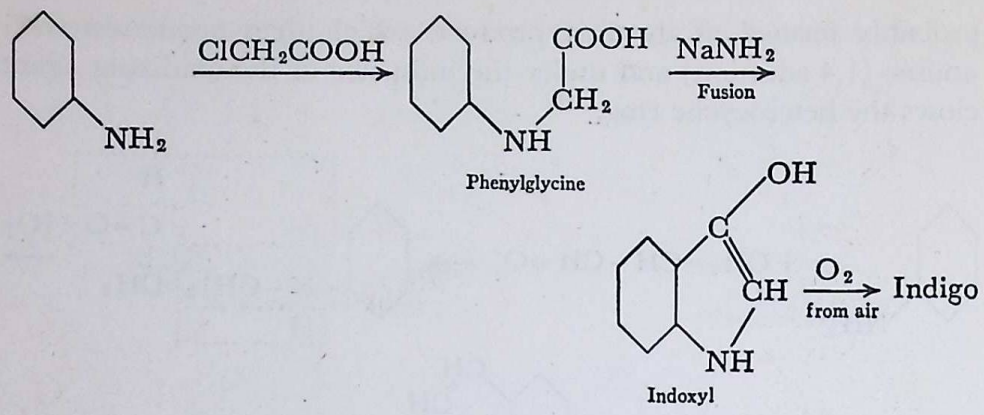
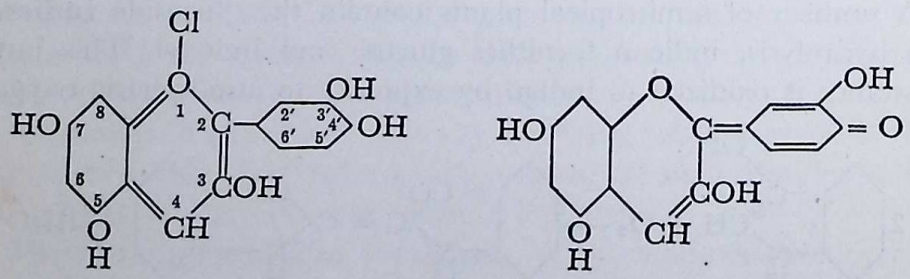


The first product of the fusion is probably the ketonic form of indoxyl.

Next to sulfur black, indigo is the most important single organic dye. The synthetic material has driven out the natural dye almost completely. In the United States in 1944 the production of synthetic indigo amounted to almost 3,500,000 lb.

The Anthocyan Pigments. The brilliant red and blue coloring materials of flowers, fruits, and variegated leaves are glucosides, known as *anthocyans* or *anthocyanins*. The residual colored substances left after removal of the sugars by hydrolysis are known as *anthocyanidins;* they all contain the same carbon skelton, that of a benzopyrilium salt, and differ only in the number of hydroxyl groups. The commonest anthocyanidin is **cyanidin chloride,** which has the following structure and which will serve to show the common carbon skeleton.



Cyanidin chloride red

Blue-violet

In the oxonium salt form, all the anthocyanidins and the corresponding anthocyans are reddish; when treated with alkali they pass into a blue or violet form which probably contains a quinonoid

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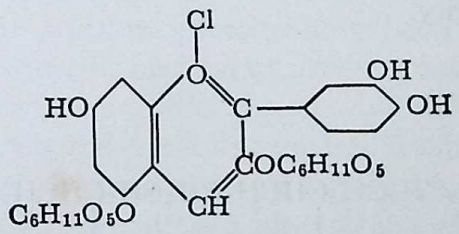
grouping (last formula above). On further treatment with alkali, the phenolic hydroxyl group forms a metallic salt which is bluish. The change of structure on passing from acid to alkaline solution should be noted.

The other two common anthocyans found in nature are **pelargonidin chloride** and **delphinidin chloride.** They differ from cyanidin chloride only by the number of hydroxyl groups on the phenyl group attached to the 2 position of the heterocyclic ring. Thus, in pelargonidin chloride there is only one OH group in the 4′ position, while in delphinidin chloride there are three in positions 3′, 4′, and 5′. These differences affect the shade of the color markedly, particularly in acid solution; pelargonidin is orange-red, cyanidin red, and delphinidin bluish red. In still other anthocyanidins, methoxy groups are present in positions 3′ and 5′.

The Color of Flowers. The anthocyanidins occur in nature combined with one or more molecules of sugar. One sugar molecule is always attached to the hydroxyl group in the 3 position. In addition an hydroxyl group at position 5 may be attached to a sugar residue. Thus cyanin, the diglucoside of cyanidin which occurs in the rose and the blue cornflower, has the following structure.



The glucose residues make the compounds much more soluble in water, of course.

Since the color of the anthocyanidins, and consequently that of the anthocyans, changes with alteration of acidity, the same pigment may serve as a reddish or a bluish coloring material. This explains the surprising fact that the same pigment occurs in both the red rose and the blue cornflower. In the rose it is present as an oxonium salt and is reddish; in the cornflower as a potassium or calcium salt and is bluish. It has been found that the color and shade of a flower (or berry) depend on: (1) the anthocyan which is present (mixtures often occur); (2) the acidity of the cell sap; (3) the presence of certain other pigments (yellow flavones) and colorless complex substances which seem to affect the shade (copigments).

The **flavonols** are a group of yellow pigments which occur as glucosides, and are therefore soluble in water. They often occur with the anthocyans in the cell sap. The relation between them and the anthocyanidins is illustrated by the following transformation which can be brought about in the laboratory and may possibly occur in nature.

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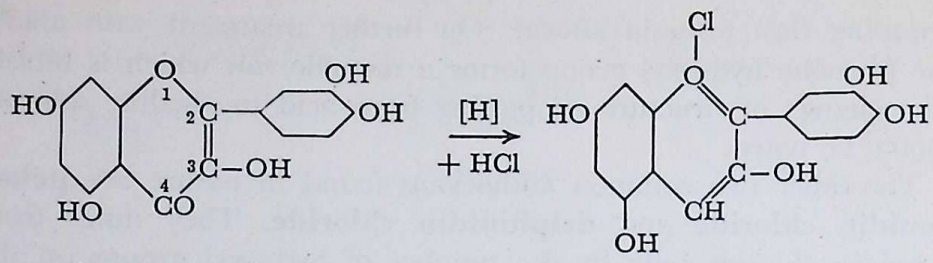
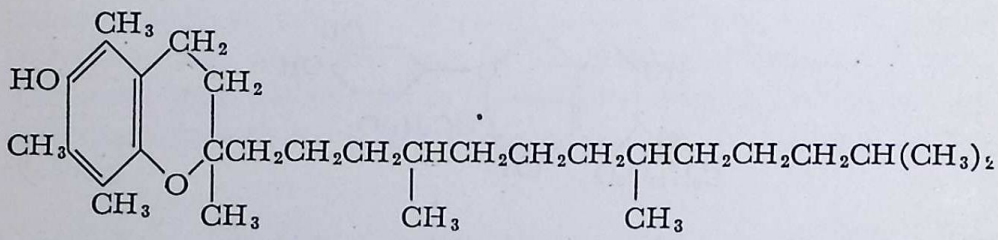


Quercetin, a flavonol; yellow

Cyanidin chloride, an anthocyanidin red (blue in alkali)

The **flavones** are another group of yellow coloring materials occurring as glucosides. They differ from the flavonols only in the presence of a hydrogen atom instead of an hydroxyl group in position 3. The yellow color of the flavones and flavonols is extremely weak and usually masked completely by the anthocyans or the pigments of the chloroplast. It was at one time thought that the flavones and flavonols were precursors in nature of the anthocyans. It now seems more probable that some unknown colorless compound is a common precursor of all three types of compounds.

Vitamin E. This vitamin, obtained from seed-germ oils, is necessary for reproduction in rats. It consists of three closely related chromans known as α-, β-, and γ-tocopherol; all three have been synthesized. A large number of related chromans show comparable physiological activity.



α-Tocopherol

PURINES

Many compounds are known in which two or more heterocyclic rings are fused together. This type of structure is found in a number of substances produced in nature. One or two important classes of substances of interest to the biochemist contain the purine system, which is composed of a pyrimidine ring and an imidazole ring fused together. The structural formula for the parent substance is written in the first formular on page 617 according to three different conventions. At first sight the reader may have difficulty in recognizing the identity of these formulations. The one on the extreme left in which a six-membered ring is written in the form of a rectangle has been

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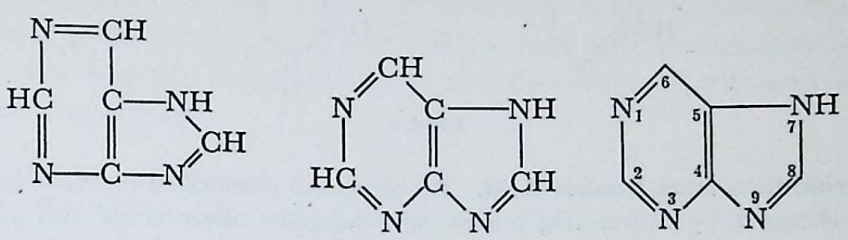
employed by almost all chemists for many years. The use of this convention tends to obscure the relationship of the purines to other aromatic, heterocyclic compounds. In recent years an increasing

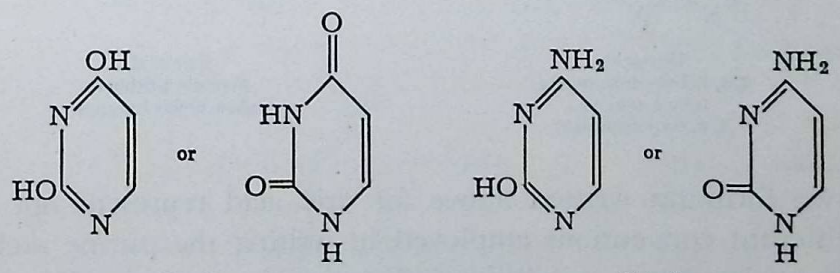


Three ways of writing the structural formulas of purine

number of chemists have employed such formulas as that shown on the extreme right. The reader should master both methods in order to be able to read rapidly in the biochemical literature.

Nucleic Acids. Very complex acids containing phosphorus occur widely distributed in plant and animal cells; they are known as the *nucleic acids*. They often occur together with certain proteins (Chap. 19), either as salts or perhaps joined by an amide linkage. Such combinations of nucleic acid and proteins have been designated as the *nucleoproteins;* they occur in particularly large amounts in the thymus and pancreatic glands of animals. A somewhat different nucleic acid is present in plant cells and is readily prepared from yeast. The nucleoproteins are important constituents of the nuclei of both plant and animal cells although their precise physiological function is not yet understood.

On hydrolysis, the nucleic acids yield phosphoric acid (H_3PO_4), a molecule of a pentose, and five heterocyclic nitrogen compounds: cytosine, uracil, thymine, guanine, and adenine. The first three substances are derivatives of pyrimidine, the last two are derivatives of purine.



Uracil

Cytosine

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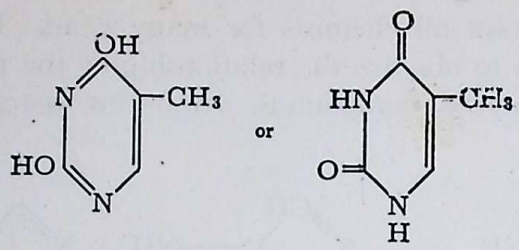
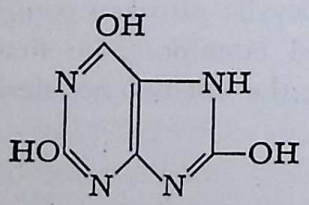


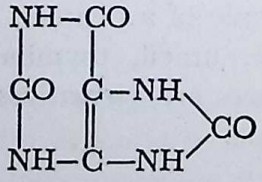
Thymine

Pyrimidines from Nucleic Acid. The structural formulas of the three pyrimidines obtained by hydrolyzing nucleic acid are given above in the two possible tautomeric forms. (See the discussion of barbituric acid, p. 606. Structural formulas of guanine and adenine are to be found on p. 621.) Since these hydroxy pyrimidines contain the grouping =N — COH = N — or NHCONH, they may be thought of as cyclic derivatives of urea, and are sometimes called *cycleic ureides* (see p. 330).

Uric Acid. The nucleic acids, which probably occur in all living cells and which decompose in the course of the oxidation reactions necessary for life, and the purine constituents in certain mammals including man are transformed largely into uric acid. Under ordinary conditions only very small quantities of uric acid are found in the urine and body fluids of the higher animals. Under certain pathological conditions, however, large quantities of uric acid are produced in man and are deposited as the sparingly soluble sodium salt. Such deposits occur in the joints and produce the unpleasant symptoms characteristic of gout. Urinary calculi which may form in the bladder also contain uric acid, and the acid was isolated from such material as long ago as 1776 by Scheele. The ammonium salt of uric acid is the chief constituent of the excrement of reptiles, birds, and insects.



Uric acid.
2, 6, 8-Trihydroxypurine
(also known as
2, 6, 8-trioxypurine)



Uric acid.
Formula written to
show ureide linkages

The two formulas written above for uric acid represent not only two different conventions employed in writing the purine skeleton but two tautomeric possibilities. Tautomeric isomers of hydroxy

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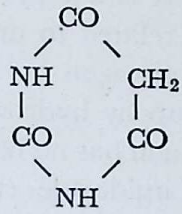
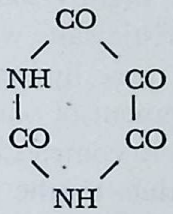
purines have never been isolated. The situation is very similar to that encountered in the hydroxy pyrimidines (see barbituric acid, p. 606).

Uric acid is a white, crystalline solid very slightly soluble in water. It is a weak, dibasic acid; the monosodium salt is difficulty soluble in water but the disodium salt is readily soluble. Uric acid has no basic properties.

Structure of Uric Acid. On oxidation uric acid is converted into alloxan and urea, NH_2CONH_2. Alloxan may also be made by the oxidation of barbituric acid (p. 331).

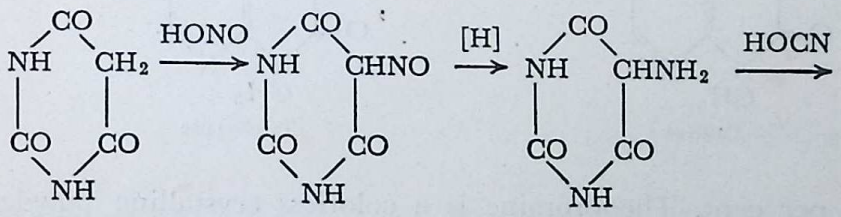


Barbituric acid

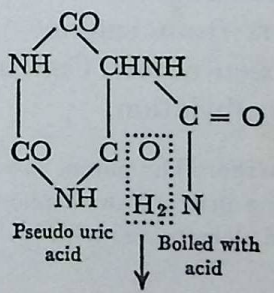


Alloxan

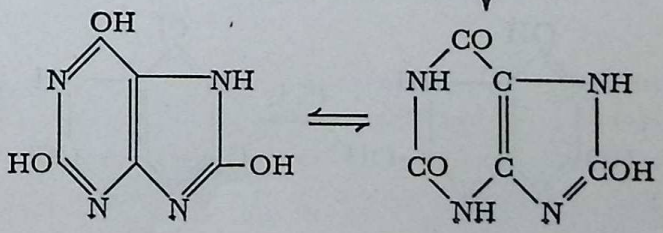
Since alloxan and urea are the oxidation products of uric acid, it is probable that the original molecule contained the skeleton of alloxan and, in addition, another ring containing a urea linkage. The proof of the structure of uric acid was finally accomplished by its synthesis by the following series of reactions.



Barbituric acid



Pseudo uric acid



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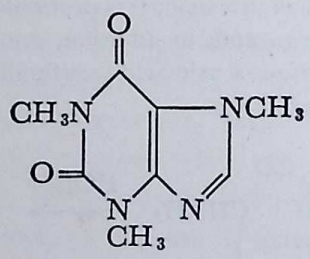
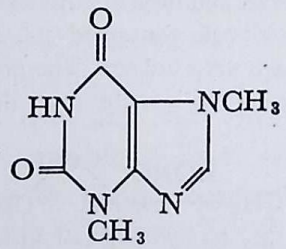
The history of the investigation of the structure of uric acid covers almost the whole classical period of organic chemistry. The greatest knowledge of the subject is due to the work of Liebig and Wöhler over a hundred years ago (1838). Baeyer in 1863 prepared pseudo uric acid (see above), but it was not till 1897 that Emil Fischer succeeded in finding the right conditions for converting this compound into uric acid itself. No other compound has had the honor of being the subject of investigation by four such masters of the science of organic chemistry.

Caffeine. This close relative of uric acid which occurs in coffee and tea to the extent of a few per cent is used in medicine as a stimulant and diuretic. It crystallizes from water in silky needles which melt at 237°. It is only slightly soluble in water. It is a very weak base but forms characteristic salts with acids. It is related to uric acid by the substitution of three hydrogen atoms on nitrogen by methyl groups and the replacement of one hydroxyl group by hydrogen. The weak basic properties in contrast to uric acid (which has no basic properties) are probably due to the fact that the imidazole ring carries no hydroxyl group. **Theobromine** is present in cocoa beans to the extent



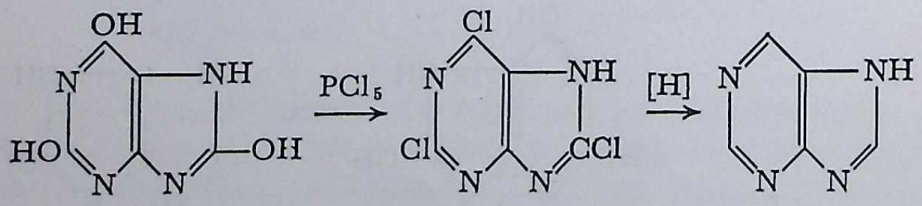
Caffeine



Theobromine

of a few per cent. Theobromine is a colorless crystalline powder which melts at 337° and which is only slightly soluble in water. It differs from caffeine in having only two methyl groups on the nitrogen atoms. Caffeine is prepared industrially from theobromine by methylation.

Purine. The parent substance of the purines can be prepared from uric acid by treating uric acid with phosphorus pentachloride, and reducing the trichloro compound thus formed with hydrogen iodide, followed by zinc.



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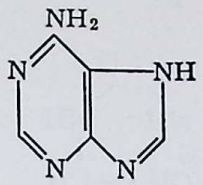
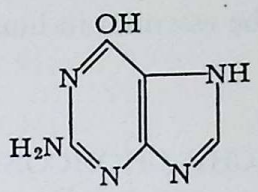
Adenine and Guanine. The two purine derivatives obtained by hydrolysis of nucleic acid have the following structures (or that of the tautomeric isomer).



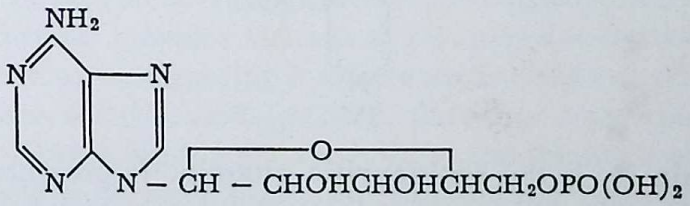
Adenine



Guanine

In the nucleic acid from yeast each of the purine derivatives is combined in position 9 with a sugar, *d*-ribose (p. 285), which in turn carries a phosphate radical on the terminal atom. Such a combination of nitrogen compound, sugar, and phosphoric acid is called a *nucleotide;* the phosphorus-free glycoside is designated a *nucleoside.* In the nucleic acids four or more nucleotides are linked together, probably through oxygen atoms of the phosphate group. They are really polynucleotides.

An example of a mononucleotide is **adenylic acid,** which occurs in muscle tissue both as such and combined with a molecule of pyrophosphoric acid (adenylic acid pyrophosphate or adenosine triphosphate). The pyrophosphate can be lost and gained reversibly in stepwise fashion under the influence of enzymes. The role of adenosine triphosphate (ATP), adenosine diphosphate (ADP), and adenylic acid (AMP) in the metabolism of carbohydrates was discussed earlier, p. 386.



Adenylic acid

On alkaline hydrolysis, adenylic acid loses phosphoric acid and passes into the nucleoside **adenosine.** On acid hydrolysis, the glycoside linkage to nitrogen is cleaved and adenine is set free. The glycosidic linkage is apparently attached in position 9 though it was formerly believed that the other nitrogen of the imidazole ring (position 7) was involved.

Xanthine and Hypoxanthine. In the animal body enzymes are present which bring about the deamination (replacement of NH_2 by OH) of adenine and guanine (or their derivatives, such as adenylic acid). The corresponding mono- and dihydroxypurines are known as *hypoxanthine* and *xanthine*, respectively. They are weaker acids than uric acid, and since the imidazole ring carries no OH group, they show weak basic properties even in aqueous solution.

The B Vitamins. The material originally obtained from yeast and other natural sources and called the *water-soluble B* fraction, has been found to consist of a number of substances differing widely in chemical structure and complexity. Among them *p*-aminobenzoic acid (p. 502),

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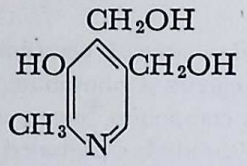
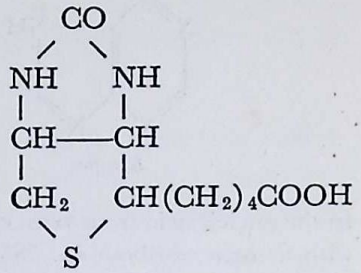
inositol (p. 573), pantothenic acid (I), pyridoxin (II), and biotin (III) have been shown to have vitamin activity, but have not been shown to be essential in human nutrition.

$CH_2OHC(CH_3)_2CHOHCONHCH_2CH_2OH$

I

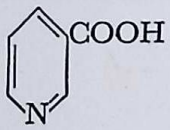


II



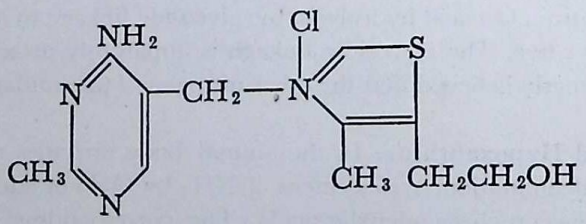
III

Three members of the B group have been established as essential in human nutrition. They are nicotinic acid and nicotinic amide, vitamin B_1 (thiamin), and vitamin B_2 (riboflavin). **Nicotinic acid,** which prevents pellagra, is pyridine-3-carboxylic acid (IV). It can be obtained by the oxidation of the alkaloid, nicotine (p. 629).



IV

Vitamin B_1 is the **antineuritic vitamin.** It prevents beriberi in man and polyneuritis in animals. Its structure, which has been established by degradation and synthesis, is:



Thiamin is a quaternary ammonium salt of a substituted thiazole (p. 599); the group attached to the heterocyclic quaternary nitrogen atom contains a pyrimidine ring. The compound is isolated as a hydrochloride, 1 mole of HCl being bound by the aminopyrimidine nucleus. Vitamin B_1 is now manufactured by synthetic methods.

Vitamin B_2 or Riboflavin is a crystalline, orange-yellow solid which exhibits a characteristic green fluorescence in solutions. It is a

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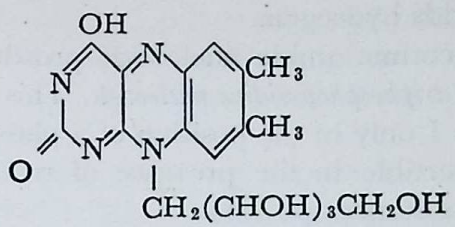
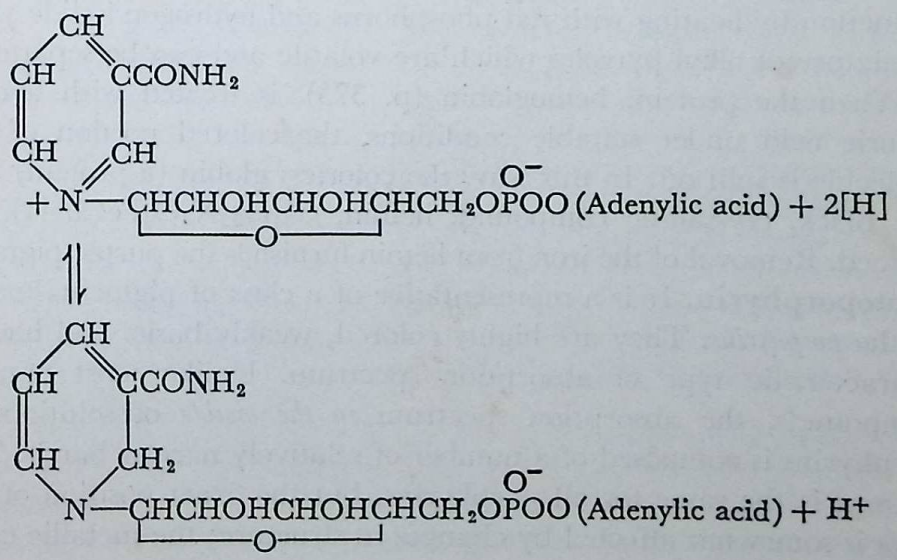
component of a respiratory enzyme system present in living cells. It is essential for growth in chicks and rats.



Riboflavin

The group attached to one of the two central nitrogen atoms is a reduced *d*-ribose molecule (ribityl). The ring system contains an oxy-pyrimidine and an ortho xylene ring fused on both sides of 1,4-diazine (p. 599).

Nicotinic Amide Nucleotides. Derivatives of nicotinic acid amide are important in the oxidation of carbohydrates by living cells (p. 395). The enzyme referred to above which dehydrogenates 1,3-diphosphoglyceric aldehyde contains as a prosthetic group a nicotinamide nucleotide often referred to as *cozymase*, or *coenzyme I*, or *diphosphopyridine nucleotide*. Attached to specific proteins it functions in a number of the enzymatic changes involved in carbohydrate metabolism. The somewhat complex formula of this pyridine derivative can be best understood by regarding it as an anhydride of two phosphoric acid esters, one adenylic acid (p. 621), the other a pyridinium salt in which the alkyl group is a pentose residue and the ion a phosphate group attached to the same sugar. The formula may then be written in simplified form as:



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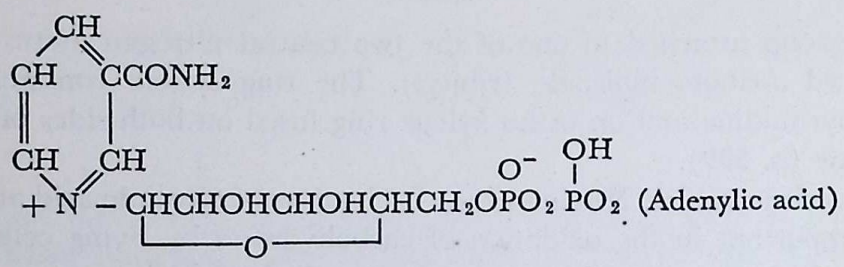
The essential chemistry of this prosthetic group involves the reversible reduction of the ring of the pyridinium salt which, unlike the pyridine ring, easily adds hydrogen.

Another nicotinic amide nucleotide prosthetic group is known as *coenzyme II* or *triphosphopyridine nucleotide*. This compound differs from the coenzyme I only in the position of a phosphate residue. The two are interconvertible in the presence of reversible enzymatic phosphorylating substance (p. 384).



POLYNUCLEAR PYRROLE PIGMENTS

Chlorophyll, the green material involved in the process of photosynthesis, and hemoglobin, the red coloring material of blood, both owe their color to a combination of four pyrrole nuclei joined in a complex molecule. **Chlorophyll** contains a magnesium atom, and **hemoglobin** an iron atom. Both metallic atoms are similarly joined to colored molecules as complex salts. The magnesium is readily removed from chlorophyll by the action of dilute acids; the iron is much more tightly bound in hemoglobin. Both pigments on vigorous reduction by heating with red phosphorus and hydrogen iodide yield a mixture of alkyl pyrroles which are volatile and can be separated.

When the protein, hemoglobin (p. 373), is treated with hydrochloric acid under suitable conditions, the colored portion of the molecule is split off. In this way, the colorless globin (a protein) and the black, crystalline compound, hemin, $C_{34}H_{32}N_4O_4FeCl$, (I), are formed. Removal of the iron from hemin furnishes the purple pigment **protoporphyrin.** It is a representative of a class of pigments known as the *porphyrins*. They are highly colored, weakly basic, and have a characteristic type of absorption spectrum. Unlike most organic compounds, the absorption spectrum *in the visible* of solutions of porphyrins is composed of a number of relatively narrow bands. The pattern is the same for all porphyrins, but the exact position of the lines is somewhat affected by changes in structure; the metallic com-

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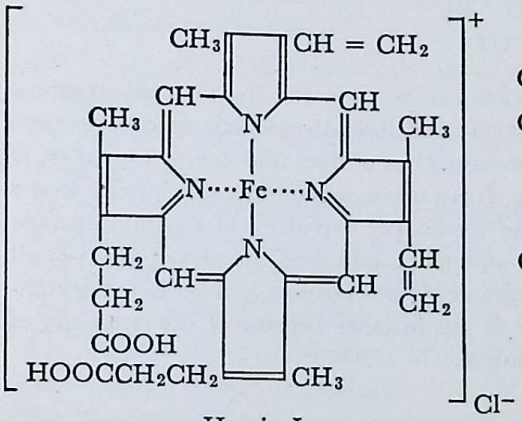
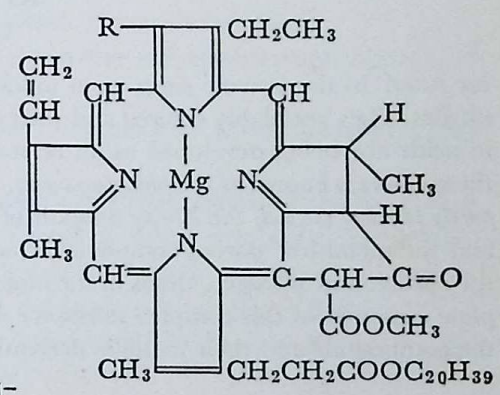
pounds such as hemin have a different type of banded spectra. Porphyrins have been found in small quantities in both the animal and plant kingdoms. In certain rare diseases, porphyrins are produced in quantity and excreted in the urine. These porphyrins differ from protoporphyrin in the nature of the groups attached to the group of pyrrole nuclei.

The two chlorophylls present in the chloroplast are known as *chlorophyll a* and *chlorophyll b*. Their basic structural skeleton (II) is the same as that in hemin. They differ from each other only in that chlorophyll b has an aldehyde group where chlorophyll a has a methyl group. Degradation of chlorophyll leads to a porphyrin.



Hemin I



II
Chlorophyll (a) R = CH_3
(b) R = CHO

All the porphyrins may be considered as derivatives of a parent substance (III) in which all the R's are hydrogen. The parent substance is named *porphin*. In **protoporphyrin** R_1, R_3, R_5, R_8 are methyl groups, R_6 and R_7, CH_2CH_2COOH groups, and R_2 and R_4, vinyl groups. The porphin ring consisting as it does of four pyrrole nuclei joined together is an essentially aromatic structure. Different arrangements of double linkages can be written without shifting an atom or group. No isomers corresponding to such formulas have ever been found, however. There is undoubtedly a good deal of resonance energy which imparts to the porphin ring a marked stability.

Porphyrins readily form metallic derivatives in which the two hydrogen atoms on two of the four nitrogen atoms are replaced by metal. A model of the porphin ring shows that all four pyrrole rings and connecting $-CH=$ groups lie in a plane. The space between the four nitrogen atoms is thus like a hole in a doughnut in which various metallic atoms readily fit.

Compounds containing rings of the porphin type but with nitrogen atoms ($-N=$) substituted for the $-CH=$ links have been prepared from simple pyrrole compounds. Like the porphyrins they contain a large planar aromatic ring, are highly colored, and form relatively stable, colored, complex metallic derivatives. The compounds in

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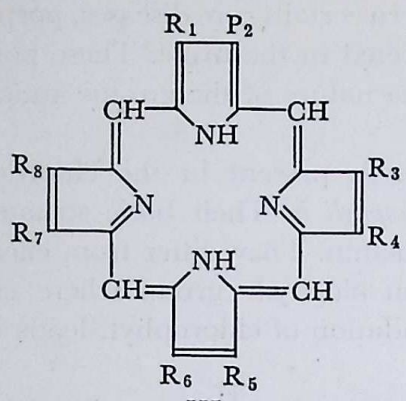
which all four links are —N= are known as the *tetra-azoporphyrins*. Substances containing this structure and having phenyl groups as substituents on the pyrrole rings



III

(or fused to the pyrrole rings as in indole) can be prepared from certain aromatic nitriles. They are highly colored and their metallic derivatives which are very resistant to acids are being developed as an important class of dyes and colors. One class of these colors is known as the *phthalocyanines*. It is a matter of considerable interest that a *purely physical method*, the X-ray analysis of the copper derivative of a phthalocyanine and the metal-free parent compound, completely established the arrangement of all the carbon and nitrogen atoms in the molecule. It was possible to determine the complete structure of this complex substance in this instance because of the symmetry of the compounds and their metallic derivatives.

QUESTIONS AND PROBLEMS

1. Write structural formulas for 2,5-dimethylfuran, N-ethylpyrrole, thiophene, 2-chloropyrimidine, 2-methylthiazole, α-methylindole, 2,4,6-trihydroxypyrimidine, acridine, xanthine, 2-hydroxypurine.

2. Write equations for (*a*) the Knorr synthesis of 2,4-dimethyl-3,5-dicarboxypyrrole from acetoacetic ester, (*b*) the Skraup synthesis of quinoline, and (*c*) the synthesis of 2,4,6-trimethylpyridine from aliphatic compounds.

3. Write the structural formulas of indigo and indigo white, and explain how indigo is applied to cotton cloth.

4. Give the systematic names (indicating position of substituents by numbers) of the following: thymine, barbituric acid, piperidine, caffeine, cytosine, adenylic acid.

5. Outline the steps in the synthesis of alloxan and uric acid from urea and aliphatic compounds.

6. Which of the following substances do you think will combine with hydrochloric acid to form a salt in dilute aqueous solution? Which will react with dilute sodium hydroxide to form a salt? Theobromine, alloxan,

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2,3-dimethylpyrrole, tetrahydropyrrole, benzoylpiperidine, N-methylpiperidine, imidazole, 2-oxypyrimidine, uric acid.

7. By analogy with pyridine write equations for the reactions to be expected when quinoline is treated with methyl iodide, and the product is treated first with alkali and then with an oxidizing agent.

8. Write a general formula for a nucleotide. What reagent would you employ to prepare from such a substance: (*a*) nucleoside, and (*b*) the heterocyclic compound?

9. Write the structural formula for 4-methyl-5-(β-hydroxyethyl) thiazole. Given this substance and 2-methyl-5-cyano-6-aminopyrimidine, by what steps would you attempt to synthesize vitamin B_1?

10. What is vitamin B_2? How does it differ from the respiratory enzyme, flavoprotein? What reagents would you employ to bring about the reduction and oxidation of riboflavin in dilute, neutral, aqueous solution?

11. Write the reactions for all the steps in the exhaustive methylation of 3-methylpyrrolidine.

12. Discuss briefly the occurrence and chemistry of the anthocyans and anthocyanidins.

13. Define and illustrate the term *pseudo base*. From which of the following substances can pseudo bases be prepared and by what methods: N-methylquinoline chloride, 2-methylpyridine chloride, 2-methylpyrimidine hydrochloride, 2,4-dimethylpyrylium chloride, benzopyrylium bromide?

14. Discuss the tautomerism of barbituric acid. Write the formulas for the tautomeric forms of adenine.

15. Write full electronic formulas (showing all the valence electrons) for the three resonating structures of pyrrole.

16. When 5-methylimidazole is treated with an alkylating reagent which brings about the substitution of a hydrogen atom in a $>$NH group by an alkyl group, two isomers are obtained. What are their formulas and how do you explain their formation?

17. Predict, with reasons for your predictions, whether 2-aminoquinoline and 4-hydroxypyridine would be more or less basic than aniline and phenol, respectively?

18. Write structural formulas for the B vitamins. Which ones are essential in human nutrition?

19. Write the structural skeleton that is common to hemin, chlorophyll. and the phthalocyanins. Explain what these materials are.

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Chapter 32

NATURAL AND SYNTHETIC DRUGS

The *materia medica* of the medical profession a hundred years ago was based on the accumulation of generations of experience in regard to the physiological action of inorganic chemicals and natural drugs. The latter substances were particularly valuable, and have remained so to the present day. During the last sixty years these natural drugs have been supplemented, but not supplanted, by a number of synthetic products. Both the old and the new remedies are used by the modern physician.

In tracing the modern history of drugs two quite different lines of development are to be noted. One was the synthesis of a multitude of new substances in the organic laboratory. When these substances were tested, certain of them were found to be valuable. Two examples will suffice: phenacetin and aspirin. The other was the study of the natural products themselves: the isolation of the active ingredients and the study of their chemical structure. As a result of this work, the constitution of many of the natural drugs was slowly revealed. Although the commercial synthesis of most of the well-known natural drugs has not yet been accomplished, a knowledge of the structure of the natural products has led to the manufacture of related synthetic products which have proved to be of great value.

We have already considered a number of synthetic drugs which are produced from aromatic compounds; for example, aspirin and other derivatives of salicyclic acid (p. 504). It only remains, therefore, to consider some of the natural drugs, and certain rather complicated products whose synthesis has been inspired by a knowledge of the action and structure of the natural substances.

Alkaloids. The name *alkaloid* is usually restricted to a group of basic, nitrogenous plant products which have a marked physiological action. The majority of these are complex, heterocyclic compounds. In recent years, certain bases isolated from animal tissues have been sometimes included in the alkaloids. The basic properties of the alkaloids are due to the presence of amino groups or trivalent nitrogen

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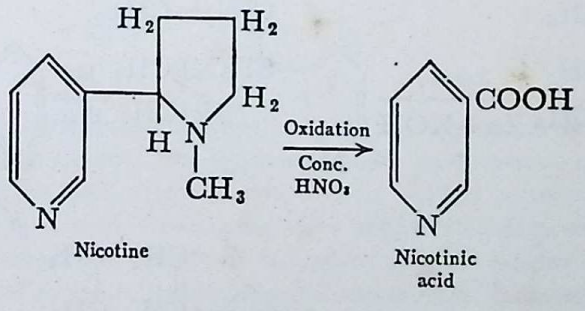
atoms which are part of a heterocyclic system. The plant alkaloids have a bitter taste and are almost all laevorotatory. They are extracted from the plants by using dilute acids in which they dissolve because of the formation of soluble salts. Their purification is often an elaborate process. They are usually sold in the form of the water-soluble chlorides or sulfates; the free alkaloids are for the most part crystalline solids which are only very slightly soluble in water.

Nicotine, which is the principal alkaloid of tobacco, is one of the simplest of the alkaloids. It is also one of the few liquid alkaloids. Nicotine is found in the tobacco plant combined with citric and malic acids (page 237), the amount of nicotine in the leaves varying between two and eight per cent. Nicotine is highly toxic. It is used as an insecticide on plants and animals.

The molecular formula of nicotine is $C_{10}H_{14}N_2$. The structural formula is given below. It will be seen that the molecule contains two heterocyclic rings; one is a pyridine ring, the other a completely hydrogenated pyrrole ring (pyrrolidine ring) with a methyl group attached to the nitrogen atom. On vigorous oxidation the five-membered ring is broken and the β-carboxylic acid of pyridine, **nicotinic acid,** is formed.



The structure of nicotine follows from two oxidative cleavages of the molecule. Direct oxidation with nitric acid (as given above) shows that the compound contains the pyridine ring with an attachment on the beta carbon atom. If the quaternary ammonium salt is formed by adding methyl iodide to the pyridine ring (p. 610) the six-membered ring becomes sensitive to oxidation in alkaline solution because the pseudo base (p. 611) is easily oxidized to a ketonic group. The resulting compound no longer contains the resistant, aromatic, pyridine ring and on oxidation with chromic acid the six-membered ring is destroyed. The structure of the reduced pyrrole thus formed can be established by synthesis and the complete structure of nicotine follows.

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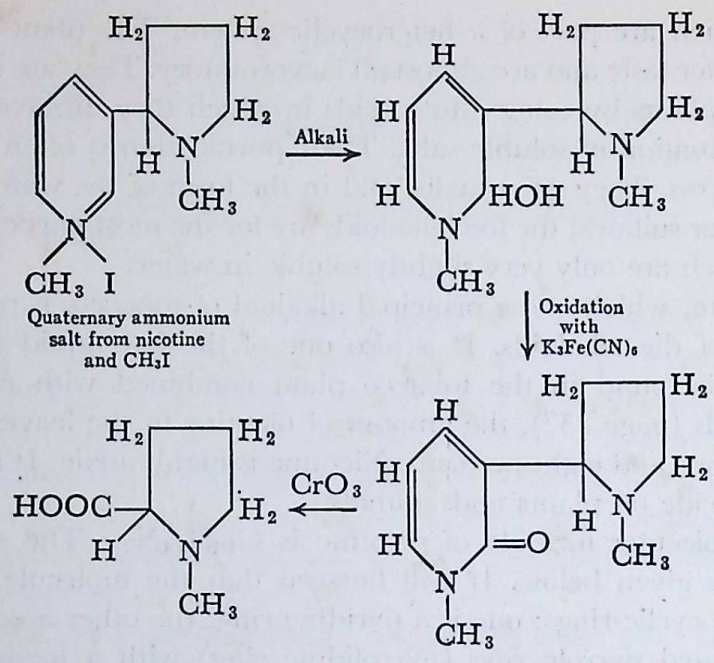
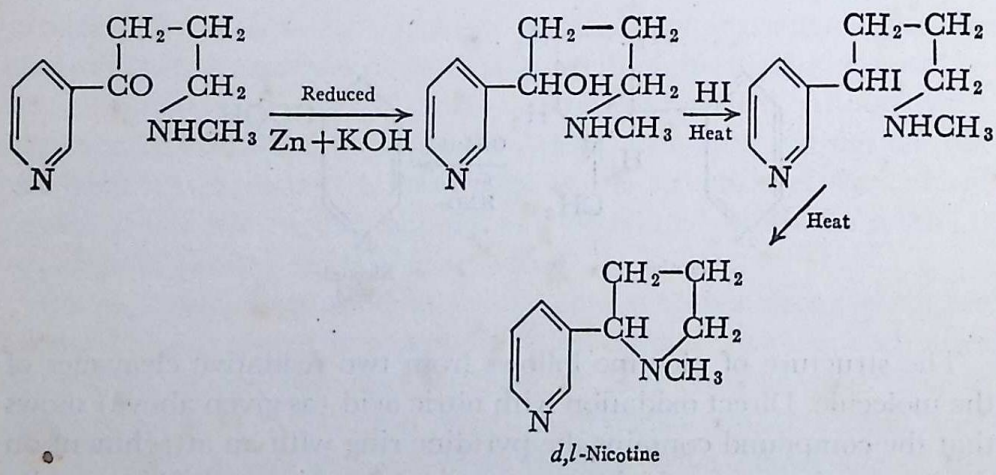


Synthesis of Nicotine. Nicotine has been synthesized by several methods. In one, an open-chain, amino-keto derivative of pyridine is cyclized by the following reactions:



Natural nicotine is laevorotatory (the beta carbon atom of the five-membered ring through which the pyridine nucleus is attached is asymmetric). The synthetic alkaloid is, of course, the racemic mixture. This can be separated by crystallizing the salts with an optically active acid as described in Chap. 13.

Cocaine. One group of drugs is composed of those which act as *local anesthetics*. These substances when injected under the skin produce

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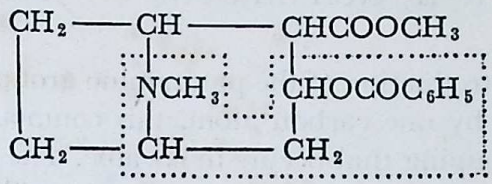
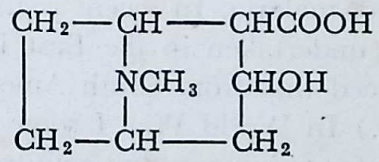
local insensibility to pain. For years the alkaloid cocaine was the only important drug of this type. It is extracted from the leaves of the *coca plant* which grows in the semitropics. (The coca plant should not be confused with the cacao bean from which cocoa and chocolate are prepared.) Cocaine, like many alkaloids, is usually marketed as one of the salts (e.g., the hydrochloride). The salts unlike the alkaloid itself are soluble in water.

Cocaine has the following structure.



On hydrolysis the two ester linkages are readily broken, the products being methyl alcohol, benzoic acid, and an hydroxy acid called *ecgonine*. The structure of ecgonine has been established both by degradation and synthesis.



Ecgonine

Ecgonine is not symmetrical. There are therefore a number of different stereoisomers possible (eight in all). The synthesis usually produces two racemic mixtures. On resolution by the usual methods, one of these yields a laevorotatory compound which on benzoylation and esterification with methyl alcohol produces the natural alkaloid cocaine. From the other pair of isomers **psuedo cocaine** can be prepared which is not very different in its physiological action from the natural alkaloid. This synthesis has been employed commercially. The industrial production of this rather complicated natural product is one of the striking feats of the synthetic chemist.

Procaine. A study of cocaine and other substances has led pharmacologists to the conviction that the grouping

$$>N - C - C - C - OCOC_6H_5$$

present in cocaine is largely responsible for its physiological action. (This grouping has been enclosed in dotted lines in the formula.) A number of new compounds have been synthesized which are simpler than cocaine and which contain this grouping or the similar

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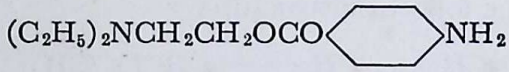
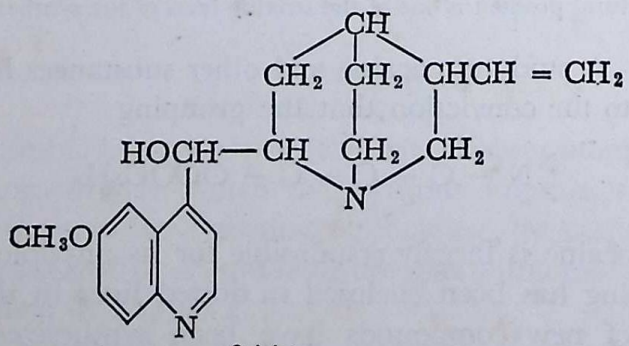
one $>N - C - C - OCOC_6H_5$. These have been found to be local anesthetics of considerable value and several have been put on the market.

The most successful synthetic local anesthetic is **procaine (novocaine).** This is used as the hydrochloride which is soluble in water; the free base has the following structure.



Except for the introduction of the para amino group and the shortening of the chain by one carbon atom, this compound has the same characteristic grouping that occurs in cocaine. The raw materials for the synthesis of procaine are para nitrobenzoic acid, ethylene chlorohydrin, and diethylamine.

Quinine and Synthetic Antimalarials. Quinine, together with a number of related alkaloids, is found in the bark of the cinchona tree, native to South America. It has been used for over three hundred years in the treatment of malaria. In recent years the cultivation of the cinchona tree was undertaken in the East Indies and quinine from this source displaced that from South America. (The parallel with rubber is striking.) In World War I some work was done in Germany on substitutes for quinine as that country was shut off from external sources of supply by the Allied blockade. This work was continued successfully in the period between wars. In World War II the cinchona plantations of the East Indies were seized by the Japanese, so that intensive efforts had to be made in the United States and the British Empire to replace quinine. The problem was particularly acute in World War II as so much of the war was fought in malaria-infested areas.



Quinine

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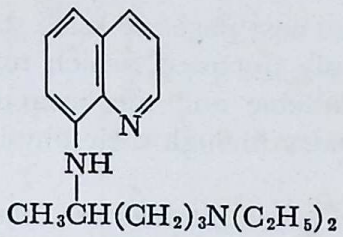
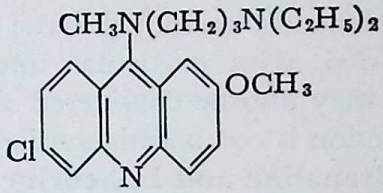
The British-American effort did not aim at the synthesis of quinine. The synthesis has been accomplished; but, as can be seen from the complexity of the quinine molecule, it is not likely to be of practical value. Instead this effort was toward the development of synthetic materials which would be equivalent to or superior to quinine. German work had led to two antimalarials: Plasmochin and Atebrin.

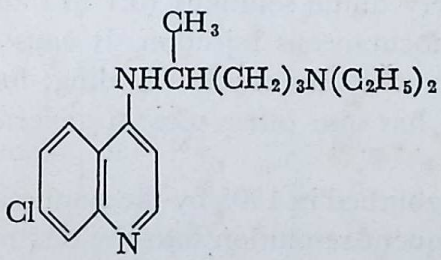


Plasmochin



Atebrin

The work in the Allied countries involved testing for antimalarial activity a large number and variety of compounds already on hand in academic and industrial laboratories, as well as the preparation and testing of many new compounds which it was hoped would be effective. The work led to the development of a number of promising antimalarials. The structural formulas of two of these developed in the United States are shown below.



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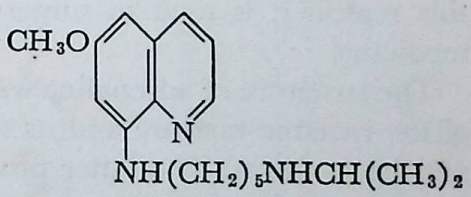

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An interesting aspect of all this work on antimalarials is that quinine, for which synthetic substitutes were being sought in the same way that novocaine was developed as a substitute for cocaine, does not prevent malaria and is curative for only certain types of malaria. A radically different approach, therefore, was the search for organic compounds which were not necessarily related to fragments of the quinine molecule and would not be expected to have quinine activity,

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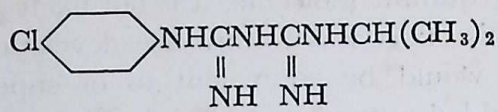
but which might have preventive or curative action or both. One of the developments along this line is Paludrine, synthesized in England.



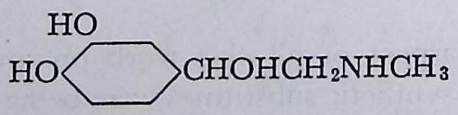
Paludrine

Other Alkaloids. In the table on the next page are listed some of the alkaloids, including those previously discussed, which may be regarded as of particular interest. Caffeine and theobromine (p. 620) may also be considered as alkaloids although their physiological action is comparatively slight.

Adrenaline and Ephedrine. These two substances are relatively simple natural bases which were formerly not classified as alkaloids, although they have a powerful and very important pharmacological action. Adrenaline is one of the active principles secreted into the blood stream by the *suprarenal glands* (see also p. 593). The production of this hormone in the animal organism has great physiological importance; its prime function appears to be to reinforce the action of the sympathetic nervous system.

The isolation of adrenaline from the suprarenal glands obtained from slaughtered animals provides the physician with one of his most valuable drugs. It is employed in very dilute solutions (0.1 to 0.01 per cent) and is administered by subcutaneous injection. It causes local contraction of the blood vessels and thus checks bleeding; for this reason it is used in surgery. It has also other uses in general medicine.

The structure of adrenaline was established in 1905 by the synthesis of the racemic mixture and its subsequent resolution into the dextro and laevo forms. The latter proved to be identical with the natural drug.



A comparison of the physiological activity of the dextro and laevo forms has shown that the latter is by far the more active. This is an illustration of the general principle mentioned in Chap. 13; although enantiomorphs are chemically identical, they usually differ in their relation to living things.

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SOME OF THE COMMON ALKALOIDS

Name of Class	*Type of Rings Containing Nitrogen*	*Common Representatives*	*Source*	*Physiological Action*
Conium alkaloids	Hexahydropyridine	Coniine	Hemlock herb	Very poisonous; paralysis of motor endings of nerves
Pepper alkaloids	Hexahydropyridine	Piperine	Pepper	Local irritant only
Tobacco alkaloids	Pyridine and tetrahydro-pyrrole	Nicotine	Tobacco	Very poisonous
Belladonna alkaloids	Tropine type	Atropine	Belladonna	Dilates pupil of the eye; very poisonous
Ergot alkaloids	Indole and reduced pyridine condensed	Ergotoxine	Certain fungi parasitic on rye	Contracts the uterus
Coca alkaloids	Tropine type	Cocaine	Coca leaves	Local anesthetic
Cinchona alkaloids	Quinoline + condensed reduced pyridine	Quinine	Bark of the cinchona tree	Specific for malaria
Opium alkaloids	Reduced pyridine condensed with reduced phenanthrene	Narcotine Morphine	Opium poppy	Narcotics
Strychnine alkaloids	Complex; complete structure still uncertain	Strychnine	Seeds of Nux Vomica	Very poisonous; in small doses increases blood pressure

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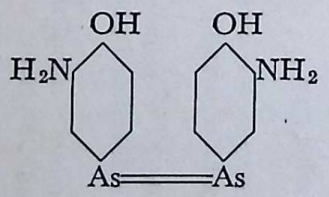
Adrenaline is now manufactured both by extraction from suprarenal glands and by synthesis. The racemic mixture obtained by synthesis must of course be separated into the optically active isomers. The substance is sold as the hydrochloride since it is more soluble in this form, and the solutions are more stable. Adrenaline itself is a white, crystalline substance which melts at 207°.

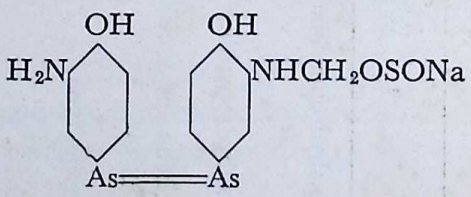
Ephedrine, $C_6H_5CHOHCH(CH_3)NHCH_3$, a very interesting plant product, finds rather wide use in medicine. This substance is closely related to adrenaline and resembles it in its pharmacological action. It is superior to adrenaline for many purposes because it can be taken by the mouth. Ephedrine is the active principle of a Chinese plant which for years has been used in China as a medicinal. Synthetic ephedrine is now manufactured in this country.

Chemotherapy. The goal of chemotherapy is to discover for each disease a chemical which will be toxic to the invading organism and harmless to the host, and which will, therefore, be a specific cure for the disease. The possibility of success in such an effort seemed best with those diseases which were caused by bacteria and protozoa which could be isolated and studied *in vitro*, and the most striking success in the early development of chemotherapy was with syphilis.

Ehrlich synthesized in the early nineteen hundreds two arsenicals—salvarsan and neosalvarsan—which proved to be extremely valuable in combating syphilis. The first compound, salvarsan, was called *606* by its discoverer because it was the 606th synthetic compound he had tried.



Salvarsan



Neosalvarsan

The synthesis of salvarsan from phenol is of some interest. Arsenic acid, H_3AsO_4, is closely related to hydrated nitric acid ($HNO_3 + H_2O = H_3NO_4$), since arsenic and nitrogen occur in the same group in the periodic table. It is therefore not surprising that phenol may be arsenated by heating with arsenic acid. The product is analogous to nitrophenol but is hydrated. A nitro group is now introduced into the molecule in the usual way and the product reduced with sodium hydrosulfite. The nitro group is thus converted to an amino group and the arsenic acid group to the arsenic analog of the azo linkage.

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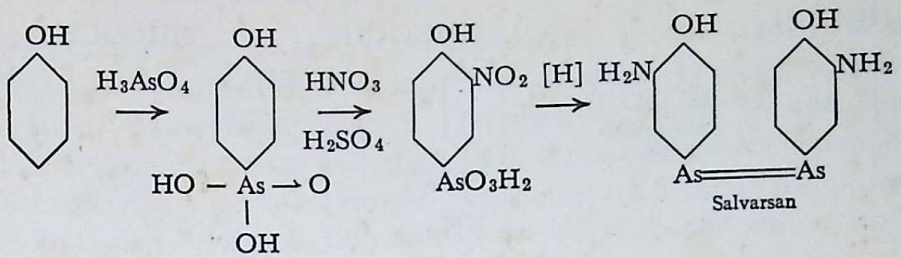
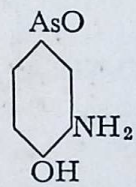
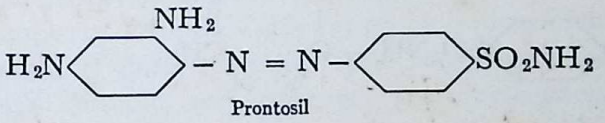


The salvarsan itself is isolated and sold as the dihydrochloride.

Ehrlich and his collaborators recognized that arsenoxide was more effective than salvarsan, but they preferred the latter material as it was apparently less toxic. More recent work has indicated that salvarsan owes its activity to oxidation to arsenoxide in the body; and that, when arsenoxide is administered in the form of derivatives which hydrolyze to form arsenoxide, it is no more toxic than salvarsan. Consequently arsenoxide is coming into extensive use in the treatment of syphilis.



Arsenoxide



Prontosil

Until recently the successful applications of chemotherapy to disease were limited to those infectious diseases caused by spirochetes (e.g., syphilis) and by protozoa. Here the results were impressive, for many of the protozoal diseases of man (sleeping sickness, amebic dysentery, leishmaniasis) can be cured by early treatment with the appropriate drugs. The search for chemical agents for control of such bacterial infections as streptococcal, staphylococcal, pneumococcal, and others of this class was not successful, however, until some twenty-five years after the discovery of salvarsan. Then the first substance employed with striking success in treating certain coccal infections was a red dye known as *Prontosil*. Pharmacological studies showed that sulfanilamide, formed from Prontosil in the body, was responsible for the effectiveness of the dye.

Sulfanilamide is manufactured from acetanilide in the following manner.

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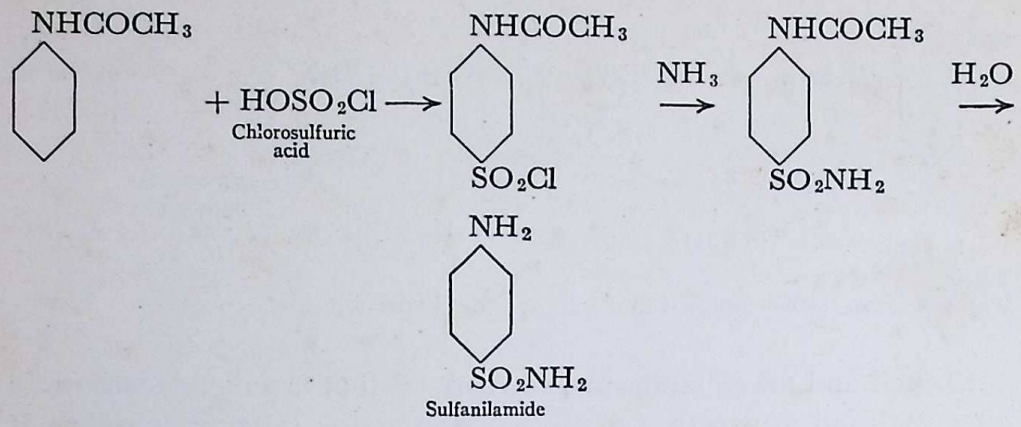
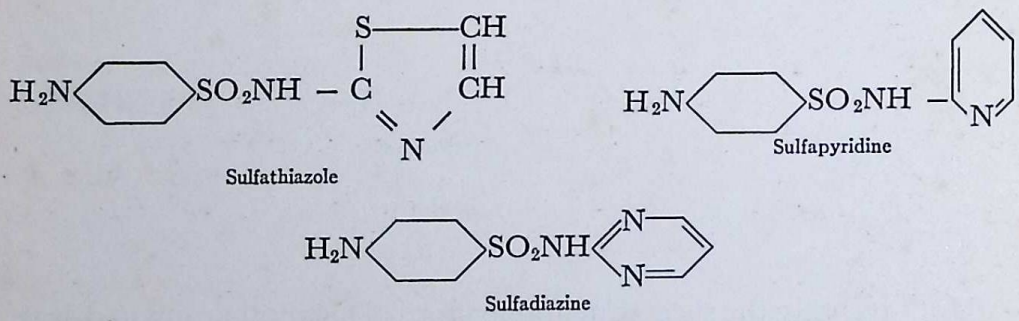


The successful use of sulfanilamide led to the preparation and study of hundreds of related compounds. Of these, **sulfathiazole, sulfapyridine,** and **sulfadiazine** are probably the most important. They have proved to be of great value against pneumococci, gonococci, and a variety of streptococcal infections.



In view of the current importance of the sulfa drugs (over 4,500,000 lb were produced in the United States in 1944) it is worth noting that sulfanilamide was first prepared at almost the same time as salvarsan (1908), and was prepared then for use in a study of the behavior of various amides on hydrolysis.

Antibiotics. A living organism may form specific substances which interfere seriously with the metabolic processes of other organisms. These substances are known as *antibiotics* and much effort has been spent on attempts to use them in the treatment of bacterial infections. The early efforts were unsuccessful: the materials used were only weakly antibacterial and were highly toxic. The first antibiotic to be used successfully is penicillin, formed by the mold *penicillium notatum.* This material is remarkable both for its great antibacterial activity and its low toxicity. Up to the present time penicillin, actually a group of related compounds, has been prepared by cultivation of the mold and extraction of the active material. Chemical studies indicate

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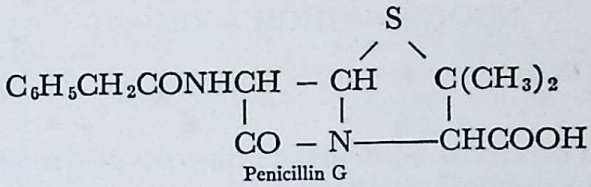
that the structure of one of the penicillins is that shown below; synthesis has furnished a product from which small amounts of penicillin G have been isolated. The current interest in antibiotics, stimulated by the results with penicillin, is comparable to that shown in the sulfa drugs ten years earlier. We may expect, therefore, progress both in the study of penicillin and in the isolation and study of other antibiotics.



Penicillin G

QUESTIONS AND PROBLEMS

1. Outline a synthesis of procaine from toluene, ethylene oxide, and ethyl alcohol.

2. Ephedrine and adrenaline have similar pharmacological action. To what part of the molecule might this action be attributed?

3. Coniine has the empirical formula $C_8H_{17}N$; on oxidation (dehydrogenation) with silver acetate, it yields a weakly basic compound, $C_8H_{12}N$, which on oxidation with chromic acid produces pyridine-α-carboxylic acid. On exhaustive methylation and hydrogenation of the resulting unsaturated hydrocarbon, coniine gives *n*-octane. What is the structure of coniine?

4. 2-Methylpyridine condenses with aldehydes to form unsaturated compounds. Utilizing this fact, outline a synthesis of racemic coniine from 2-methylpyridine.

5. Write structural formulas for sulfanilamide, sulfathiazole, sulfadiazine, and sulfapyridine.

6. What reactions would you use to convert ecgonine to cycloheptanone?

7. Discuss briefly the development of synthetic antimalarials. Write structural formulas for two such materials.

8. The development of synthetic drugs has often taken the following path: isolation of the active ingredient of a naturally occurring drug; determination of the structure of the active ingredient; synthesis of the active ingredient; synthesis of materials structurally related to the active ingredient. Show the status in this scheme of each of the following materials: penicillin, novocaine, quinine, plasmochin.

9. Define and illustrate each of the following terms: *alkaloid*, *chemotherapy*, *antibiotic*.

10. How many stereoisomers of ephedrine are possible? What might you obtain in a synthesis from optically inactive material? How would you

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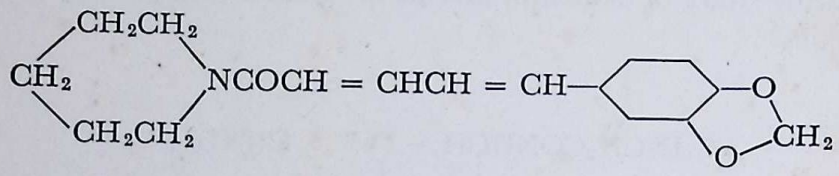
prepare the optically active drug from such a product? Starting with propionic acid, benzene, and methylamine, outline the steps in the synthesis of racemic ephedrine.

11. Write equations for the steps in the preparation of 3-aminopyridine from nicotine.

12. Piperine, the alkaloid from pepper, has the following structure:



What would you predict as to the basic properties of this alkaloid? By what reactions could its structure be established?

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